Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 2- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the in vitro bacterial reverse-mutation assay, the in vitro bacterial DNA repair assay, the in vitro forward gene mutation assay in mouse lymphoma cells, the in vitro chromosomal aberration assay in Chinese hamster lung (CHL) cells, the in vivo micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats.

Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the in vitro chromosomal aberration assays in CHL cells with and without metabolic activation. **2,3-DCPP produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained** in the in vivo micronucleus assay in mice; **however, the response was shown to be due to a mechanism not considered relevant to humans.**

Impairment of fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy

Pregnancy Category C

In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the **maximum recommended human dose** [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal

development as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg~~;~~ (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, **likely** mediated through effects on female offspring) was seen at 30 mg/kg

Some maternal toxicity was seen at 30 mg/kg; however, there ~~is~~ **was no** evidence to suggest that ~~all~~ **the** developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), ~~and~~ increased incidence of a skeletal abnormality (fused sternebrae **at 30 and 100 mg/kg**), and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole peri- and post-natally (from day 17 of gestation through day 21 post-partum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused

once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are13 and 19 times the maximum recommended human dose, based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC.

Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed.

The relevance of this finding to human risk is unknown.

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ON ORIGINAL

APPENDIX 1

Date: October 28, 2002

To: Lois Freed, CDER

From: James T. MacGregor, Ph. D., D.A.B.T.

Subject: Comments on Otsaka Pharmaceutical Company Micronucleus Test of OPC-14597 in ICR Mice (Study No. 018330)

The purpose of the study was to determine if the increase in bone marrow micronucleus frequency observed after oral treatment with OPC-14597 could be prevented by maintaining animals in a heated caging environment that prevented hypothermia from developing in the treated animals. Because it has previously been shown that the micronucleus induction generated by reserpine could be prevented by maintenance of body temperature, reserpine treated animals were included for comparison so that the response to both OPC-14597 and reserpine could be shown to be comparable.

The study was well designed and well conducted. The report is clear, logical, and includes all relevant data.

The study achieved the stated objective, and demonstrated that both OPC-14597 and reserpine induced a significant increase in micronuclei in reticulocytes of bone marrow of mice housed in wire cages without any special environmental control. Monitoring body temperature demonstrated that treated animals became hypothermic. When mice were housed in heated polycarbonate cages with wood-chip bedding, body temperature loss after treatment was markedly less, and neither OPC-14597 nor reserpine induced a significant and consistent increase in micronucleated reticulocytes in bone marrow.

Some technical comments and caveats:

- The protocol states that bone marrow smears were fixed in ethanol. The usual fixative for bone marrow smears is absolute methanol. Is the protocol correct, and if ethanol was in fact the fixative, has the staining quality of the slides been verified? The negative and positive control values obtained are comparable with the published literature, so the data does not suggest any significant problem with the procedure employed.

- Although only one sampling time was used following a single dose of test agent, the fact that both bone marrow and peripheral blood were scored provides the equivalent of two sampling times in either tissue alone (due to the earlier appearance of micronucleated cells in bone marrow relative to peripheral blood). Thus, the sampling protocol provides a valid test.

- Dose solution analysis verifies the stability and homogeneity of the test articles.

- General criteria for validity of the test preformed are met satisfactorily.

- It would have been valuable to have metabolism and pharmacokinetic data from both test conditions, to enable a determination of whether a temperature effect on metabolism could have contributed to the observed effect.

- There is a suggestion of a possible slight increase in the frequency of micronuclei in bone marrow of the female mice even under the heated cage condition, but the possible effect is equivocal and is clearly greatly reduced compared to the group in unheated wire cages.

- The *in vitro* data should be carefully evaluated to determine if there is any indication of a genotoxic potential of OPC-14597. In the absence of any such indication, I would concur with the interpretation that the apparent increase in micronuclei in the unheated wire-caged group is likely an indirect effect related to maintenance of body temperature.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lois Freed
11/8/02 10:51:31 AM
PHARMACOLOGIST

Barry Rosloff
11/8/02 03:17:12 PM
PHARMACOLOGIST

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Pharm / Tox

Labeling Recommendations

CLINICAL PHARMACOLOGY

Pharmacodynamics

Aripiprazole exhibited high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7 and 3.4 nM, respectively); and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM respectively) and the serotonin reuptake site (K_i = 98 nM). Aripiprazole had no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1000 nM). Aripiprazole functioned as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown.

Aripiprazole's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

Aripiprazole's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for two years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] on a mg/m^2 basis, respectively). In addition, SD rats were dosed orally for two years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD on a mg/m^2 basis). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.5 to 5 times the MRHD on a mg/m^2 basis). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (3 times the MRHD on a mg/m^2 basis); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (19 times the MRHD on a mg/m^2 basis).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies.

However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole was clastogenic in *in vitro* chromosomal aberration assays in CHL cells with and without metabolic activation and in the *in vivo* micronucleus assay in mice.

Impairment of fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

PREGNANCY

Pregnancy Category C

(Note to sponsor: doses causing fused vertebrae in rabbits may be changed pending submission of historical control data)

In animal studies aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rat and rabbit.

Pregnant rats were treated with oral doses of 3, 10 and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and

delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules (liver protrusion through the diaphragm) and diaphragmatic hernia (30 mg/kg; the other dose groups were not examined for these finding). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Slight maternal toxicity was seen at 10 and 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (6, 19, and 65 times the MRHD on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), and an increased incidence of skeletal abnormalities (fused sternebrae) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole peri- and post-natally (from day 17 of gestation through day 21 post-partum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILITAT (aripiprazole) is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILITAT misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in rats in a 26-wk chronic toxicity study at a dose of 60 mg/kg and in a 2-yr carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose on a mg/m^2 basis. The relevance of this finding to human risk is unknown.

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Note to sponsor: please provide (1) interspecies comparisons based on AUC [where available] for the findings described in labeling. Comparisons between plasma exposures in animals and human should be made based on comparable AUC data in humans at the 30-mg dose. If possible, comparisons should be provided for both extensive and poor metabolizers. (2) the data you used to make these comparisons.

PRECAUTIONS

Retinal pathology in albino rats: Retinal degeneration was observed in albino rats in a 26-wk oral toxicity study and in the 2-yr carcinogenicity study. Evaluation of the retinas of albino mice and of monkeys did not reveal similar changes. Additional studies to further evaluate the specific pathology have not been performed. The potential significance of this effect in humans has not been established [see ANIMAL TOXICOLOGY].

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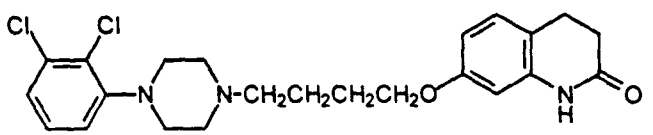
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: **21-436**
Review number: **1**
Sequence number/date/type of submission: N-000, 10/31/01
Information to sponsor: Y
Sponsor and/or agent: Otsuka Pharmaceutical Co., Ltd
2-9 Kanda tsukasa-cho
Chiyodo-ku Tokyo, 101-8535, Japan
Manufacturer for drug substance: Otsuka Pharmaceutical Co., Ltd.
Reviewer names: Lois M. Freed, Ph.D.
Sonia Tabacova, Ph.D. [reproductive and developmental toxicology studies]
Division name: Neuropharmacological Drug Products
HFD #: 120
Review completion date: 8/19/02
Drug:

Trade name: [ABILITAT]
Generic name (list alphabetically): aripiprazole
Code name: OPC-14597, OPC-31, BMS-337039, BMS-337039-01
Chemical name: 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydro-2(1H)-quinolinone
CAS registry number: 129-22-12-9
Mole file number:
Molecular formula/molecular weight: 448.39
Structure:



Relevant INDs/NDAs/DMFs: [redacted]
Drug class: partial D_2 and $5HT_{1A}$ agonist, $5HT_2$ antagonist
Indication: schizophrenia
Clinical formulation: 10, 15, 30 mg tablets
Route of administration: oral
Proposed use: n/a
Studies previously reviewed:

PK/PD
Toxicology
acute [Sprague-Dawley rat, cynomolgus monkey]
3-mo + 4-wk recovery [Sprague-Dawley rat, cynomolgus monkey]
1-yr [Sprague-Dawley rat, cynomolgus monkey]
dose-range finding [ICR mouse]
dose-range finding [Fischer rat]
Reproduction
Segment I [Sprague-Dawley rat]
Segment II [Sprague-Dawley rat, New Zealand rabbit]
Genotoxicity
Ames test
in vitro chromosomal aberration assay [CHL cells]
in vivo micronucleus assay
DNA repair

Studies reviewed in this submission:

- Pharmacology [Vol .1.16-18]
- Safety Pharmacology [Vol 1.18-1.21]
- PK/ADME [Vol 1.22-1.36]
- Toxicology (TK)
  - Acute [rat (i.v.), monkey (i.v.); Vol 1.46-1.48]
  - Subchronic [4-wk monkey (p.o., Vol 1.56)]
  - Chronic [26-wk rat (p.o., Vol 1.51-1.55), 39-wk monkey (p.o., Vol 1.57-1.61)]
- Special Toxicology
  - acute irritation [dermal, rabbit (Vol 1.114), eye, rabbit (Vol 1.114), i.m., rat (acute: Vol 1.115, 2-wk: Vol 1.116), i.m., rabbit (Vol 1.117)
  - antigenicity [guinea pig, Vol 1.117]
  - immunotoxicity [4-wk rat, Vol 1.117]
  - mechanistic studies [Vol 1.118-1.121]
    - serum prolactin [mouse (acute p.o., 4-wk p.o., 13-wk p.o.), rat (acute, 1-wk p.o., 4-wk p.o., 13-wk p.o. (with 4-wk interim report), 1 study - duration not specified)]
    - hormones [13-wk p.o., rat]
    - dependence [4 studies, Vol 1.122]
  - metabolites [6 studies, Vol 1.122]
- Carcinogenicity (TK)
  - 104-wk study [mouse, Vol 1.67-1.70]
  - 104-wk supplemental study [mouse, Vol 1.71-1.73]
  - mouse tumor-incidence [supplemental statistical analysis, Vol 1.74]
  - 4-wk dietary TK study [mouse, Vol 1.75]
  - 104-wk study, 2 studies [rat, Vol 1.75-1.79 and Vol 1.80-1.106]
- Reproduction
  - Male fertility [rat, Vol 1.109]
  - preliminary teratogenicity [rat, Vol 1.110; rabbit, Vol 1.112 (two studies)]
  - teratogenicity [rat, Vol 1.110-1.111; rabbit, Vol 1.113]
  - acute-dose [non-pregnant rabbit, Vol 1.112]
  - preliminary perinatal and postnatal [rat, Vol 1.114]
  - perinatal and postnatal [rat, Vol 1.114]
- Genotoxicity [Vol 1.65-1.66]
  - Ames test
  - *in vitro* mouse lymphoma
  - *in vitro* chromosomal aberration
  - *in vivo* micronucleus assay [mouse]

Previous reviews:

- Review and Evaluation of Pharmacology and Toxicology Data: original summary [redacted] Steven Sparenborg, Ph.D., 8/4/93]
- Review and Evaluation of Pharmacology and Toxicology Data: mouse and rat dose-range-finding study results and carcinogenicity study protocols [redacted], Steven Sparenborg, Ph.D., 1/14/94]
- Review and Evaluation of Pharmacology and Toxicology Data: Submission #030 [redacted] Steven Sparenborg, Ph.D., 4/14/95]
- Review and Evaluation of Pharmacology and Toxicology Data: Rev 1, Supplement No. N096 [redacted]; Lois M. Freed, Ph.D., 6/26/97]
- Pharmacology/Toxicology Memorandum to [redacted] [Lois M. Freed, Ph.D., 2/12/97]

Pharmacology/Toxicology Memorandum — Lois M. Freed, Ph.D., 11/17/97]
Pharmacology/Toxicology Memorandum — Lois M. Freed, Ph.D., 1/8/98]
Pharmacology/Toxicology Memorandum — Lois M. Freed, Ph.D., 11/1/99]

Disclaimer: Tabular and graphical information from sponsor's submission are identified as such; quoted text is designated by quotation marks.

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Executive Summary

I. Recommendations

From a pharmacology/toxicology standpoint, the data are adequate to support approval of the NDA. However, it is recommended that the sponsor conduct additional studies [as a postmarketing commitment] to address the following issues: (a) characterization and, if possible, the mechanism(s) underlying the retinal degeneration observed in the 26-wk chronic toxicity and the 2-yr carcinogenicity studies in Sprague-Dawley rat and (b) the potential abuse liability of aripiprazole.

II. Summary of Nonclinical Findings

The pharmacology of aripiprazole is complex. In *in vitro* receptor binding assays, aripiprazole exhibited highest affinity for the D_2, D_3, and $5HT_{1A}$ receptors, although high affinity was also exhibited for the $5HT_{2A}$ and $5HT_{2C}$ receptors. In some *in vitro* and *in vivo* functional assays, aripiprazole exhibited partial agonist activity at the D_2 and $5HT_{1A}$ receptors. However, aripiprazole did not induce rotational behavior in several animal models of dopamine receptor supersensitivity, suggesting a lack of D_2 agonist effects. In other assays, aripiprazole exhibited activity consistent with D_2 and $5HT_2$ antagonist effects. The major human metabolite, OPC-14857 [aka BMS-337044] exhibited high *in vitro* binding affinity for the D_2 and D_3 receptors, and, in functional assays, exhibited both D_2 agonist and antagonist effects. In safety pharmacology studies, aripiprazole had clear effects on neurological [e.g., sedation] and cardiovascular function. In anesthetized dog, aripiprazole exhibited cardiostimulatory effects [e.g., increased heart rate, CO] at lower doses, but either an attenuation or reversal of these effects at the high dose tested. The effects on QT were inconsistent, i.e., "slightly" prolonged QT in one *in vivo* study, decreased QT with no change in QT_c in another *in vivo* study. Aripiprazole's effect on the I_{Kr} channel was not assessed. Aripiprazole had no effect on renal function in rats, but inhibited GI transit in mice. Studies conducted in rat and monkey suggest that aripiprazole may have some abuse/physical dependency liability. One of 4 monkeys trained to self-administer cocaine continued to self-administer when aripiprazole was substituted for cocaine. Following abrupt cessation of dosing, withdrawal symptoms were observed in 4 of 4 monkeys.

PK/ADME studies indicated metabolism of aripiprazole was qualitatively similar in mouse, rat, monkey, and human.

In subchronic and chronic toxicity studies, a number of target organs were identified. However, only the CNS was identified as direct target organ common to both rat and monkey [based on clinical signs]. Following chronic administration in the rat, other target organs included adrenal gland [hypertrophy], pituitary gland [atrophy], mammary gland [hyperplasia, secretion], male and female reproductive organs, lung [phospholipidosis], and eye [retinal degeneration]. [These findings were also observed in the carcinogenicity study in rat conducted at doses of 10-60 mg/kg.] The sponsor considered a number of effects observed in the chronic rat study to be secondary to elevations in serum prolactin or body weight/food consumption effects. In monkey, the only other notable toxicity was the presence of gallstones/"gallsand" in bile, liver, and gallbladder. Analysis of the material indicated the presence of conjugated metabolites. The extent of conjugation of metabolites and the elimination of conjugated metabolites in bile was demonstrated to be markedly higher in monkey than in rat, mouse or human.

The carcinogenic potential of aripiprazole was tested in mouse and rat. In mouse, pituitary gland adenomas and mammary gland tumors [adenoacanthomas, adenocarcinomas] were detected at doses of 3, 10, and 30 mg/kg. In rat, mammary gland fibroadenomas were detected at 10 mg/kg in a study conducted in Fischer 344 rats [1, 3, 10 mg/kg]. Mammary gland tumors were not observed in the second study conducted in Sprague-Dawley rats using gavage administration [10, 20, 40, 60 mg/kg]. In Sprague-

Dawley rat, adrenocortical tumors [adenomas, combined adenomas and carcinomas] were increased at 60 mg/kg. The mammary gland tumors were considered related to elevations in serum prolactin. Serum prolactin was not measured in the carcinogenicity study; however, a number of special toxicology studies were conducted in order to assess the effects of aripiprazole on serum prolactin levels at doses relevant to the carcinogenicity findings. The data were somewhat inconsistent. Overall, the data in mice would suggest that serum prolactin is elevated at the doses associated with pituitary and mammary gland tumors. However, serum prolactin was not elevated in Fischer 344 rats in either 4- or 13-wk dietary studies, including at the dose associated with mammary gland fibroadenomas. In contrast, serum prolactin was shown to be elevated at the doses used in Sprague-Dawley rats, the strain in which an increase in mammary gland tumors was not observed. The adrenocortical tumors in Sprague-Dawley rat were attributed to cytotoxic effects of aripiprazole on the adrenal gland, resulting in increased cell proliferation and tumors. [Increased cell proliferation in adrenocortical cells (collected in the carcinogenicity study) was detected in both male and female Sprague-Dawley, although adrenocortical tumors increased only in females.] A number of non-neoplastic findings were observed in the carcinogenicity study in Sprague-Dawley rat, including sciatic nerve degeneration [60 mg/kg], skeletal muscle atrophy [20-60 mg/kg], lung phospholipidosis [20-60 mg/kg], testicular atrophy/degeneration and epididymal spermatogenic cell degeneration [40-60 mg/kg].

The nonclinical data on aripiprazole were difficult to interpret in terms of mechanism since the serum prolactin effects were inconsistent and toxicity findings suggested both agonist and antagonist effects. For example, both pituitary atrophy, a D_2 agonist effect, and mammary gland stimulation [e.g., hyperplasia, secretion], a D_2 antagonist effect, were observed at similar doses in females. Also, in a special study conducted in order to assess the effects of aripiprazole on serum prolactin, increases in serum prolactin and effects on female reproductive organs were observed at the lower doses [and not at the high dose], whereas mammary gland effects [e.g., secretion] were dose-related.

Aripiprazole was demonstrated to be reproducibly clastogenic in *in vitro* chromosomal aberration assays in Chinese hamster lung cells, with and without metabolic activation. Aripiprazole was also positive in one of two *in vivo* micronucleus assays. The sponsor attributed the positive *in vivo* findings to aripiprazole-induced hypothermia, but did not demonstrate that prevention of hypothermia prevented increases in formation of micronuclei. Aripiprazole was negative in the *in vitro* bacterial reverse mutation [Ames], the *in vitro* bacterial DNA repair, and the *in vivo-in vitro* DNA repair assays.

Fertility and general reproductive performance (rat). Upon exposure of sexually mature male (throughout the cycle of spermatogenesis) and female rats (for about 3 estrus cycles), aripiprazole affects selectively the female reproductive function, inducing estrus cycle irregularities and ovulation disturbances down to the lowest tested dose, 2 mg/kg/day (no-effect level not reached). This dose is below the LOAEL for general toxicity in rat female, and on a mg/m^2 basis, represents about two-thirds of the maximal recommended human dose (MRHD = 30 mg/day, or 0.5 mg/kg/day for a 60-kg person). In the male, adverse effects on reproductive organs (prostate atrophy) and spermatogenesis are induced by much higher levels that are generally toxic (LOAEL = 40 and 60 mg/kg/day, or on a mg/m^2 basis, 13x and 20x MRHD, respectively). These effects do not impair fertility in either males or females, and, except for a slight (female-mediated) increase in the pre-implantation embryonic loss and a slight decrease in fetal weight, the development of the next (F1) generation is normal. The adverse effects in the female are explained as secondary to aripiprazole-induced hyperprolactinemia specific for the female rat, and are not likely to be relevant to the human because the drug does not increase serum prolactin in either women or men.

Pregnancy/Embryofetal development (rat, rabbit). Upon exposure in pregnancy during the period of organogenesis, aripiprazole has no selective effect on the prenatal development in the rat. Retarded fetal growth (demonstrated as a retarded skeletal ossification, decreased fetal weight, and retarded testes

descent) occur at LOAELs of 10 and 30 mg/kg/day, i.e. at or above the LOAEL for maternal toxicity (10 mg/kg/day). Visceral anomalies (diaphragmatic hernia and abnormal liver shape, the latter also seen in some untreated animals) occur at the maternally toxic dose of 30 mg/kg/day. However, the drug affects postnatal development at doses below those inducing maternal toxicity in the rat. Delayed sexual maturation (retarded vaginal opening) of the F1 female offspring is seen at a LOAEL of 10 mg/kg/day and is discernible in single pups even at 3 mg/kg/day. This dose, on a mg/m^2 basis, is approximately equal to the MRHD. The adequacy of these data for the human is uncertain because the rat is not an appropriate animal model for predicting the reproductive effects of aripiprazole in humans, having in mind the specific effect of the drug on prolactin in this species, as pointed out above.

In the rabbit, aripiprazole affects embryo/fetal development only at doses that are maternally toxic; therefore the drug is not a selective embryo/fetal toxicant in this species. Spontaneous abortion, lower fetal weight, and an increase in minor skeletal abnormalities are seen at a LOAEL of 30 mg/kg/day, a level corresponding to maternal exposure [AUC (0-24 h)] approximately 3 times that observed at the MRHD in humans. The highest no-effect dose is 10 mg/kg, an exposure [AUC (0-24 h)] over 2 times that observed at the MRHD in humans.

Perinatal and postnatal effects (rat). Upon exposure to aripiprazole in late pregnancy and lactation, a slight but significant delay in parturition, a significantly increased stillbirth rate, decreased early postnatal survival, and decreased weight gain of the progeny are seen at the maternally toxic dose of 30 mg/kg/day (10 times the MRHD based on body surface area). Because aripiprazole is excreted in rat maternal milk, the postnatal developmental disturbances may be due in part to a direct exposure of progeny to the drug. The highest no-effect dose is 10 mg/kg/day – a dose that, based on body surface area, is over 3 times higher than the maximal recommended human dose.

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

ARIPIPRAZOLE

Primary pharmacodynamics/Mechanism of action

Aripiprazole is characterized as a $D_2/5HT_{1A}$ partial agonist and a $5HT_2$ antagonist. It is the sponsor's position that these properties underlie aripiprazole's antipsychotic activity.

Aripiprazole was tested for *in vitro* binding to a number of receptors/binding/uptake sites. Aripiprazole exhibited high *in vitro* affinity for the D_2 receptor in rat striatum, limbic forebrain, and frontal cortex [K_i = 0.8, 0.4, and 1.4 nM, respectively. For comparison, D_2 receptor binding affinities in these tissues were provided for CPZ [12.8, 18.3, and 46.5 nM, respectively], clozapine [350, 268, and 396 nM, respectively], sulpride [332, 176, and 278 nM, respectively], and haloperidol [1.9, 1.3, and 4.0 nM]. Binding affinities at other sites were summarized in the following sponsor's table:

Table 1

Affinity of Aripiprazole for Selected CNS Receptors

CNS Receptor	Species	Aripiprazole K_i (nM)
D_3	rat recombinant	1.6
D_3	human recombinant	0.8
5-HT_{1A}	bovine	17.3
5-HT_{1A}	human recombinant	1.7
5-HT_{2A}	rat cortex	18.3, 20.1#
5-HT_{2A}	human recombinant	3.4
D_4	human recombinant	44
5-HT_{2C}	pig choroid plexus	6.5
5-HT_{2C}	human recombinant	15
5-HT_7	human recombinant	39*
α_1-adrenergic	rat frontal cortex	37.4, 56.9**
H_1	bovine	13.1
H_1	human (Hela-S3 cells)	61
5-HT reuptake site	human recombinant	98
5-HT_6	human recombinant	214•
M_1	bovine striatum	>1000
M_2	rat heart	>1000
M_3	guniea pig ileum	>1000

\# risperidone (K_i = 0.2 nM), chlorpromazine (K_i = 3.0 nM), haloperidol (K_i = 41.7 nM), clozapine (K_i = 11.1 nM).
* clozapine (K_i = 44 nM), risperidone (K_i = 2.7 nM)
** chlorpromazine (K_i = 3.2 nM), haloperidol (K_i = 38.3 nM), clozapine (K_i = 48.4 nM).
• clozapine (K_i = 10.6 nM)

(Data from BMS DCNs 920001537, 920001498, 920001499, 920008550, 920010832, 920010958)

Aripiprazole exhibited weak *in vitro* binding affinity for the α_2, $5HT_3$, σ_1, and σ_2 receptors [K_i = 791, 150, 349, and 578 nM, respectively] and for the DA and 5HT uptake sites [K_i = 678 and 236 nM, respectively]. No *in vitro* binding affinity [K_i > 10 μM] was exhibited for the adenosine A_1 and A_2, β-adrenergic, D_1, $GABA_A$, glutamate [AMPA, kainate, NMDA, glycine strychnine-sensitive], histamine H1 and H2, cholinergic muscarinic M1, M2, and M3, serotonin $5H_{1B}$, $5HT_{1D}$, and $5HT_4$, opiate [Δ, κ, μ] receptors, for the NE uptake site, or various ion channels [e.g., Ca, K, Na].

Evidence for D_2 partial agonist effects was obtained using a number of different assays. In a C-6 glioma cell line stably transfected with the rat D_{2L} receptor, aripiprazole inhibited cAMP production and isoproterenol-induced accumulation of cAMP, but to a lesser extent than dopamine. In addition, aripiprazole antagonized dopamine's inhibition of stimulated cAMP accumulation when applied in combination. Aripiprazole- and dopamine-induced cAMP accumulation was completely blocked by eticlopride, a D_{2L} antagonist.

In CHO-D_{2L} cells, aripiprazole inhibited forskolin-stimulated increases in cAMP accumulation, with a maximum effect 20% lower than that of dopamine. [Similar results were obtained in HEK-293 cells expressing the human recombinant D2L receptor.] In the presence of EEDQ, an alkylating agent used to eliminate receptor reserve, the maximum inhibitory effect was decreased. [EEDQ had a similar effect on D_2 partial agonists, S-(-)-3-PPP and terguride.] In contrast, dopamine's maximum effect was not affected. Aripiprazole, when administered with dopamine, inhibited the maximum inhibitory effect of dopamine, resulting in an inhibitory response similar to that of aripiprazole alone. In CHO-D_{2L}, aripiprazole also exhibited greater affinity for the G-protein coupled state of the receptor [K_i = 0.34 nM vs 0.7 nM for the uncoupled state]. Partial agonist, terguride, exhibited a difference in binding affinity to the 2 states similar to that of aripiprazole.

D_2 partial agonist effects were observed in primary cultures of female rat anterior pituitary cells. In one study, aripiprazole and S-(-)-3-PPP maximally inhibited prolactin release to a lesser extent than dopamine [relative efficacy: 1.0, 0.71, and 0.59]; however, aripiprazole was more potent [EC_{50} = 21, 5.7, and 82 nM for dopamine, aripiprazole, and S-(-)-3-PPP, respectively]. Haloperidol blocked the effects of all three compounds. In other studies, aripiprazole maximally inhibited prolactin release by ≈50%, whereas dopamine reduced prolactin release to ≈7% of control. When aripiprazole and dopamine were tested in combination, the degree of inhibition was similar to that obtained with aripiprazole alone. Pretreatment of cells with EEDQ reduced the magnitude of aripiprazole's effect to a greater extent than that of dopamine [from 100 to 84% inhibition for dopamine; from 69 to 45% inhibition for aripiprazole]; EEDQ also reduced the magnitude of the inhibition induced by S-(-)-3-PPP [from 54 to 34% inhibition].

In rat striatal membranes, aripiprazole inhibited the binding of ^{3}H-SCH-23390 [a D1 receptor antagonist] and ^{3}H-spiperone [a D_2 and 5HT2 antagonist]. Aripiprazole inhibited quinpirole [a full D_2 agonist]-stimulated GTPase activity. The sponsor considered this as evidence of a partial agonist effect. However, aripiprazole's effect was similar to that of sulpride, a D_2 antagonist, and aripiprazole's effect on GTPase activity was not assessed in the absence of quinpirole. In striatal membranes from rats treated for 3 wks with haloperidol [1 mg/kg p.o.], D_2 receptor density [as measured by ^{3}H-spiperone binding] was significantly increased. In contrast, aripiprazole had no significant effect on D_2 receptor density when administered at a dose of 12 mg/kg; only a small [20%] increase in ^{3}H-spiperone binding was observed following a dose of 100 mg/kg for 3 wks.

Aripiprazole exhibited agonist activity at the D_2 autoreceptor in mouse forebrain. Aripiprazole significantly inhibited DOPA accumulation in forebrain of mice treated with γ-butyrolactone [a blocker of impulse flow] and a decarboxylase inhibitor [ED_{50} = 2.8 mg/kg]. Aripiprazole also inhibited reserpine-induced DOPA accumulation [in the presence of a decarboxylase inhibitor] in mouse and rat forebrain. Tested at two different doses [3 and 0.5 mg/kg p.o.] in two separate studies, aripiprazole exerted a greater effect on reserpine-induced DOPA accumulation at the lower dose [50 vs 24%] [When given for 3 wks (0.3 mg/kg p.o.), aripiprazole (0.3-1 mg/kg p.o.) had effects on reserpine-induced DOPA accumulation similar to that after acute dosing.] Haloperidol antagonized the acute effects of aripiprazole in both models in mouse forebrain.

Evidence for $5HT_{1A}$ partial agonist effects was obtained in an *in vitro* assay in CHO cells. Aripiprazole [K_i = 1.65 nM for $5HT_{1A}$ binding in CHO cells] stimulated [^{35}S]GTPγs binding to the $5HT_{1A}$ receptor

expressed in CHO cells [EC_{50} = 2.12 nM], and exhibited intrinsic agonist efficacy of ≈68% [compared to >98% for full agonists, 5HT and 8-OH-DPAT]. [Ziprasidone had a similar effect in this assay.] Aripiprazole inhibited neuronal firing in the dorsal raphe nucleus [rat brain] following i.v. administration [1-5 mg/kg]; this effect was completely antagonized by WAY-100635. Aripiprazole decreased 5-HTP [30% at 100 mg/k p.o.] and increased DOPA in mouse forebrain. The effect on DOPA was greatest at the lower doses [3-30 mg/kg p.o.; no effect at 100 mg/kg p.o.]. The effect on DOPA would appear to be a postsynaptic D_2 antagonist effect. However, the sponsor noted that $5HT_{1A}$ partial agonist, (-)-3-PPP, has been reported to significantly increase DOPA accumulation in normal animals, and to decrease striatal DOPA in reserpine-treated animals, consistent with aripiprazole's effect.

In a series of electrophysiology studies, aripiprazole was found to exhibit (presynaptic) D_2 agonist effect as evidenced by a decrease in the firing rate of dopamine neurons in the VTA region of rat brain. [Quinpirole exhibited a similar effect.] This effect was antagonized by domperidone, a D_2 antagonist. In the N. accumbens [rat brain], dopamine and D_1 and D_2 agonists [SKF-38393 and quinpirole, respectively] inhibited firing of neurons induced by stimulation of the parafascicular nucleus. Aripiprazole had no effect alone and had no significant effect on the inhibitory effect of the agonists. Aripiprazole did significantly inhibit D_1 and D_2 agonist-induced inhibition of glutamate-induced spontaneous firing. Aripiprazole inhibited neuronal activity in the rat striatum induced by substantia nigra stimulation (as measured using *in vivo* microionophoretic techniques), as did domperidone. Aripiprazole antagonized quinpirole-induced, but not glutamate-induced, firing of striatal neurons. These data would are consistent with D_2 antagonist effects; however, the sponsor considered them evidence of partial agonist effects on the D_2 postsynaptic receptor. In rat, aripiprazole [5 mg/kg i.v.] inhibited the firing rate of 5HT neurons in the dorsal raphe nucleus, an effect that was completed antagonized by WAY100635, a $5HT_{1A}$ antagonist.

The effect of aripiprazole on monoamine turnover was assessed in rat and mouse brain. With acute dosing, increased turnover of dopamine was observed in rat frontal cortex, limbic forebrain, and striatum at 10-30 mg/kg p.o. The magnitude of the effect was similar in the three brain regions. D_2 antagonists, chlorpromazine, haloperidol, and risperidone, had similar effects on accumulation of dopamine metabolites, DOPAC and HVA. In a separate study, the effects of aripiprazole on dopamine turnover was reduced following repeated dosing [3 wks]; however, in that study, the acute effects of aripiprazole were less than in the previous study and other D_2 antagonists were not tested for comparison. Increases in dopamine turnover were also detected in mouse forebrain and whole brain following acute doses [3-30 and 10-100 mg/kg p.o. in forebrain and whole brain, respectively]. NE turnover was increased in whole brain [100 mg/kg p.o.], but was unaffected in forebrain. 5HT turnover was reduced in mouse forebrain [30 mg/kg p.o.], but was not effected in whole brain. No changes in brain levels of dopamine, NE, or 5HT were detected in either forebrain or whole brain. In mice treated with α-methyl-p-tyrosine, aripiprazole enhanced the disappearance rate of dopamine and NE in whole brain. Dopamine metabolism was assessed in the neostriatum and olfactory tubercle in mouse brain. In the olfactory tubercle, an acute dose of aripiprazole had no effect. With chronic dosing [21 days], aripiprazole increased concentrations of 3-methoxytyramine [a marker of dopamine release] and 3-MT/dopamine, as did risperidone. Haloperidol increased dopamine, 3-MT, and 3-MT/dopamine. In the neostriatum, neither aripiprazole or haloperidol had any effects on dopamine, 3-MT, or 3-MT/dopamine; risperidone decreased dopamine concentrations after both acute and chronic dosing.

In conscious, freely moving rats [using *in vivo* microiontophoresis], aripiprazole increased dopamine turnover in the striatum following acute doses of 10 and 40 mg/kg p.o, and in the prefrontal cortex at 10 mg/kg p.o. Decreases in 5HT metabolism in the striatum and prefrontal cortex were noted after acute, but not chronic, dosing. Increases in dopamine and metabolites, DOPAC and HVA, were detected in the striatum [prefrontal cortex was not examined] following chronic dosing [10, 40 mg/kg p.o.]. The sponsor

concluded that increases in dopamine turnover reflected $5HT_{1A}$ or D_2 partial agonist effects of aripiprazole.

The effect of aripiprazole [10 mg/kg p.o.] on monoamine uptake was tested in mouse forebrain. Aripiprazole had no effect on NE uptake when given alone or with H77/77 [a NE- and dopamine-depleting agent] or in dopamine when given alone. When given with H77/77, aripiprazole slightly [20%] inhibited H77/77-induced depletion of dopamine. Aripiprazole inhibited H75/12-induced depletion of 5HT by 36%. [The sponsor concluded that aripiprazole did not affect NE, dopamine, or 5HT uptake.]

In vivo studies: aripiprazole was tested in a number of *in vivo* studies in order to assess effects on dopaminergic and serotonergic functions. Aripiprazole exhibited effects similar to those of other D_2 antagonists [haloperidol, chlorpromazine, risperidone] in a number of studies. Aripiprazole significantly inhibited the increase in SMA induced by methamphetamine [0.3-10 mg/kg p.o.] in mice, apomorphine-induced SMA in rats [ED_{50} = 2.5 mg/kg p.o.], and apomorphine-induced stereotypy in mice [0.2 mg/kg p.o.] and rats [ED_{50} = 5.3 mg/kg p.o.]. Aripiprazole had no effect on spontaneous motor activity in reserpine-treated mice following acute doses of 0.3-10 mg/kg p.o. In contrast, apomorphine markedly increased SMA at doses of 0.1-0.3 mg/kg. Aripiprazole [3-30 mg/kg] did not induce contralateral rotation in rats lesioned with 6-OHDA. Apomorphine [0.25 mg/kg s.c.] did induce contralateral rotations in this animal model of denervation supersensitivity. Aripiprazole inhibited ipsilateral rotations induced in rats by administration of kainic acid [ED_{50} = 1.4 mg/kg p.o.], as did haloperidol and chlorpromazine [ED_{50} = 0.22 and 2.1 mg/kg p.o.]. These effects are not consistent with D_2 agonist effects.

Apomorphine-induced SMA was enhanced in rats pretreated for 10 days with haloperidol. When administered following a 10-day treatment with haloperidol, aripiprazole decreased SMA.

Aripiprazole inhibited head-twitching in mice induced by 5-methoxy-N,N-dimethyltryptamine [ED_{50} = 7.0 mg/kg p.o.], indicating a $5HT_2$ antagonist effect. ED_{50}'s for risperidone, chlorpromazine, and haloperidol in this model were 0.01, 1.7, and 2.7 mg/kg, respectively.

In an animal model considered to have predictive validity for a clinical antipsychotic effect, aripiprazole significantly inhibited the conditioned avoidance response in rats at doses ≥15 mg/kg p.o. Haloperidol, chlorpromazine, and clozapine also had activity in this model; D_2 autoreceptor agonist, OPC-4392, did not.

In an animal mode of conflict behavior [punished licking], aripiprazole attenuated the effect of shock in two separate studies; however, the effect-doses were not consistent between studies. In one study, aripiprazole attenuated shock-induced reductions in licking at 3, but not 10 or 30 mg/kg p.o., whereas in the other study, aripiprazole was effective at 30, but not 3 or 10 mg/kg p.o. Clozapine, similar to aripiprazole, increased punished licking; haloperidol had no effect in this model. [Aripiprazole had no effect on sensitivity to electric shock or on spontaneous drinking behavior at the doses tested.]

Side-effect liability

As noted by the sponsor, measurement of c-*fos* expression in various regions of rat brain has been investigated as possible method to distinguish antipsychotic drugs associated with eps in humans from those that do not. The sponsor compared the effects of aripiprazole, haloperidol and fluphenazine [considered typical antipsychotic drugs], and clozapine and sulpiride [considered atypical antipsychotic drugs] on *c-fos* expression in various brain regions [medial prefrontal cortex, striatum, N. accumbens, lateral septum] in male Wistar rats following acute dosing. Induction of c-fos in the dorsolateral striatum [considered to reflect eps liability] was observed following administration of haloperidol [2 mg/kg i.p.] and fluphenazine [2 mg/kg i.p.], but not with clozapine [20 mg/kg i.p.], sulpiride [100 mg/kg i.p.], or

aripiprazole [40 mg/kg i.p.]. Induction of c-fos expression n the N. accumbens [considered to reflect antipsychotic efficacy] was observed following administration of haloperidol, fluphenazine, clozapine, and sulpiride, but not aripiprazole. Robertson *et al.* [Robertson GS *et al. JPET*, 271:1058-1066, 1994] tested numerous compounds demonstrated or presumed to exhibit antipsychotic efficacy in this paradigm. All [including haloperidol, risperidone, clozapine, sulpiride, thioridazine, fluperlapine, fluphenazine, remoxipride, loxapine, molindone, chlorpromazine, and raclopride] increased *c-fos* expression in the N. accumbens. Typical antipsychotic drugs [e.g., haloperidol, chlorpromazine, fluphenazine] also induced *c-fos* expression in the dorsolateral striatum. Whereas a number of compounds considered to be atypical antipsychotics did not induce *c-fos* expression in this brain region [e.g., remoxipride, clozapine], others did [e.g., risperidone, thioridazine].

Following chronic [21 days] dosing with haloperidol in rats, apomorphine-induced stereotypy was increased compared to the effect observed in animals treated with vehicle for 21 days. Aripiprazole given for 21 days also enhanced apomorphine-induced stereotypy, although to a lesser extent than haloperidol. Haloperidol's effect was observed for 8 days following the end of the 21-day dosing period, whereas, aripiprazole's effect was not observed after Day 3.

The induction of catalepsy in animals is considered to reflect a risk of eps in humans. Aripiprazole induced catalepsy in both mice [ED_{50} = 3.5 mg/kg p.o.] and rats [50.1-73.6 mg/kg p.o.] following acute dosing. [ED_{50}'s for chlorpromazine and haloperidol were 6.7 and 0.3 mg/kg p.o., respectively, in mice and 10 and 0.7 mg/kg p.o., respectively, in rats]. Administration of aripiprazole [0.3 mg/kg] for 21 days did not affect the catalepsy response observed following oral doses of 1-10 mg/kg p.o. in mice [ED_{50} = 5.5 mg/kg p.o. following acute and chronic dosing]. However, the duration of catalepsy was found to decrease following multiple dosing [21 days] in mice. Striatal levels of DOPAC and HVA and/or ratios of these metabolites to DA were somewhat elevated following acute, but not multiple dosing. In the olfactory tubercle the acute effects were greater than in the striatum, but no increases in DOPAC, HVA, or in the ratio of these metabolites to DA were observed following multiple dosing. The sponsor compared the ED_{50}'s for induction of catalepsy and antagonism of apomorphine-induced stereotypy for aripiprazole, olanzapine, and risperidone. ED_{50}'s for catalepsy were 27.7-50, 8.5-10.4, and 9.5-7.1 mg/kg p.o. for aripiprazole, olanzapine, and risperidone, respectively. The ratios of the ED_{50}'s [catalepsy/apomorphine-induced stereotypy] were 6.5, 4.7, and 4.7 for aripiprazole, olanzapine, and risperidone, respectively. The sponsor concluded that the "catalepsy liability" was less for aripiprazole than for olanzapine or risperidone. A similar comparison was made using the ED_{25}'s for induction of ptosis [107.7, 15.9, and >5 mg/kg p.o. for aripiprazole, olanzapine, and risperidone, respectively]. The "sedation liability" ratio was 14, 7.2, and <3.3 mg/kg p.o. for aripiprazole, olanzapine, and risperidone, respectively.

Aripiprazole increased serum prolactin in male and female Wistar rats following acute dosing [3, 10, 30 mg/kg p.o.]. In males, serum prolactin was significantly increased [2-fold] only at 30 mg/kg and only at 1 hr postdosing. In females, serum prolactin was significantly increased at all doses, in a dose-related manner [≈3-5 fold].

The sponsor noted that convulsions were observed during Phase 2 clinical trials with aripiprazole. In order to further investigate the potential for aripiprazole to induce convulsions, the effects of aripiprazole on GABA- and NMDA-induced currents were tested in dissociated pyramidal neurons in neonatal [7-19 days postpartum] rat hippocampus. A whole-cell patch-clamp technique was used. Apripirazole [10^{-5} M] significantly inhibited the GABA-induced current [40%]; this effect was reversible following washout. Aripiprazole had no effect on NMDA-induced currents.

Aripiprazole had no effect on epinephrine-induced lethality in mice [32-128 mg/kg p.o.] or on NE- [up to 128 mg/kg p.o.] or physostigmine-induced [up to 300 mg/kg p.o.] lethality in rats.

Secondary pharmacodynamics:

Aripiprazole was tested in a number of *in vitro* studies in order to determined functional effects at various receptors/binding sites. The following effects were observed:

(a) aripiprazole antagonized NE-induced contractions of isolated rat aorta [male Wistar rat] [$pA_2 = 7.06 \pm 0.05$, $pD_2 = 4.95 \pm 0.04$], with no effect on resting tension. At lower concentrations, aripiprazole's inhibitory effect was characterized as competitive, whereas at the higher concentrations, it was noncompetitive. HAL exhibited similar effects [$pD2 = 6.27 \pm 0.10$].

(b) aripiprazole antagonized oxytocin-induced contractions of nonpregnant Wistar At lower concentrations, aripiprazole's inhibitory effect was characterized as competitive, whereas at the higher concentrations, it was noncompetitive [$pD2 = 4.95 \pm 0.09$] . HAL had similar effects on oxytocin-induced contractions [$pD2 = 4.92 \pm 0.07$]; however, at the highest concentration [3×10^{-5} M] HAL transiently increased resting tension.

(c) aripiprazole had no notable effect on uterine movement [amplitude, frequency] in female Wistar rats at doses of 0, 0.3, 1, and 3 mg/kg i.v.

(d) aripiprazole and HAL antagonized carbachol-induced contractions in isolated guinea pig [male Hartley] at concentrations of 10^5 and 3×10^{-5} M. HAL's effect [24 and 85%, respectively] at these concentrations was greater than that observed with aripiprazole [9 and 17% vs 8 and 15% with vehicle]. Neither drug had an effect on resting tension. Isoproterenol [the positive control] produced a concentration-related inhibition of induced contractions.

(e) aripiprazole, CPZ, and HAL antagonized ACh- and histamine-induced contraction of isolated guinea pig ileum. pA_2 and/or pD_2 values were as follows:

aripiprazole: $pA_2 = 5.59 \pm 0.10$ and 7.86 ± 0.09 for ACh- and histamine-induced contractions, respectively. $pD_2 = 4.84 \pm 0.09$ for histamine-induced contractions.
CPZ: $pA_2 = 6.51 \pm 0.11$ and 8.03 ± 0.09 for ACh- and histamine-induced contractions, respectively. $pD_2 = 5.50 \pm 0.03$ for histamine-induced contractions.
HAL: $pA_2 = 5.78 \pm 0.10$ and 6.46 ± 0.14 for ACh- and histamine-induced contractions, respectively. $pD_2 = 4.84 \pm 0.04$ for histamine-induced contractions.

Aripiprazole also inhibited barium-induced contractions [$pD_2 = 3.94 \pm 0.11$]; CPZ and HAL were not tested with this agonist.

Aripiprazole and CPZ had no effect on resting tension; HAL slightly increased resting tension at the two highest concentrations.

(f) the effects of aripiprazole on body temperature were assessed in ICR mice and rats. In male mice, aripiprazole significantly reduced rectal temperature all doses administered [50, 100, 200 mg/kg p.o.]. By the first time point examined [2 hrs postdosing], rectal temperature [°C] fell to 30.5 ± 0.64 , 29.6 ± 1.05, and 26.7 ± 0.68 at 50, 100, and 200 mg/kg, respectively. Rectal temperature remained <33° C throughout the measurement period [up to 48 hrs postdosing] at the highest dose [at 48 hrs, rectal temperature was 28.78 ± 2.37. At 50 mg/kg, rectal temperature was <33° C at 8 hrs postdosing, but was 33.38 ± 1.39° C by 19 hrs postdosing. At 100 mg/kg, rectal temperature was <33° C at 24 hrs postdosing, but was 36.06 ± 0.41° C by 48 hrs.

In male Wistar rats, aripiprazole decreased rectal temperature at doses of 100 and 300 mg/kg p.o., but not at 30 mg/kg; however, at neither of the 2 highest doses did rectal temperature fall to 33° C or below. The lowest mean rectal temperatures recorded were 35.39 and 34.48° C at 100 and 300 mg/kg, respectively. Haloperidol significant reduced rectal temperature at 100 mg/kg p.o. [mean: 35.2° C], but had no effect at 3, 10, or 30 mg/kg.

Pharmacology Drug Interaction Studies: the effects of administering aripiprazole [p.o.] with various other drugs [p.o.] on reserpine-induced increases in forebrain DOPA , apomorphine-induced stereotypy [male ICR mice], on induction of catalepsy and ptosis [male ICR mice], and on plasma prolactin levels [male Wistar rats] were assessed.

When administered alone, aripiprazole [3 mg/kg] antagonized reserpine-induced increases in DOPA in male ICR mouse forebrain [40-45%]. When administered alone, HAL and risperidone had no effect on reserpine-induced DOPA increases. CPZ alone antagonized reserpine-induced DOPA accumulation at 30 mg/kg, and lorazepam alone reduced reserpine-induced DOPA accumulation at doses of 10 and 30 mg/kg [36%]. Benztropine tended to antagonize reserpine-induced DOPA accumulation; however, the maximum effect [28% at 10 mg/kg] was not significant. There was no apparent interaction between HAL and aripiprazole or between risperidone and aripiprazole. Aripiprazole [3 mg/kg] in combination with either benztropine or lorazepam additively [or slightly less than additively] increased reserpine-induced DOPA accumulation. CPZ antagonized aripiprazole-induced inhibition of reserpine-induced DOPA accumulation.

There was no clear interaction between HAL and aripiprazole in antagonism of apomorphine-induced stereotypy. There was a synergistic antagonism of apo-induced stereotypes when aripiprazole and risperidone were given together at 1 and 0.1 mg/kg, respectively; at higher doses of risperidone, no greater effect was noted with the combination compared to risperidone alone. There was also a synergistic antagonism of apo-induced stereotypes when aripiprazole [1 mg/kg] was administered with CPZ [3 and 10 mg/kg]; at 30 mg/kg CPZ, the effect of co-administration was similar to that with CPZ alone.

The effects of HAL [0.1-1 mg/kg p.o.], CPZ [3-30 mg/kg p.o.], risperidone [0.1-1 mg/kg p.o.], benztropine [1-10 mg/kg p.o.], fluoxetine [3-30 mg/kg p.o.], and lorazepam [3-30 mg/kg p.o.] on catalepsy and ptosis was assessed in male ICR mice, when given alone and in combination with aripiprazole [10 mg/kg p.o.]. Aripiprazole, HAL, and CPZ, when given alone, significantly increased incidences of catalepsy. When HAL or CPZ were administered in combination with aripiprazole, the effect was not significantly greater than when aripiprazole was administered alone. When risperidone and aripiprazole were administered in combination, there was a tendency for the incidences of catalepsy to be increased with increasing doses of risperidone; however, the effect was not significant. Benztropine antagonized aripiprazole-induced catalepsy [significantly at 10 mg/kg], whereas lorazepam and fluoxetine had no significant effect on aripiprazole-induced catalepsy.

Aripiprazole, HAL, benztropine, lorazepam, and fluoxetine did not induced ptosis when administered alone. In addition, no ptosis was detected when aripiprazole was administered in combination with HAL, benztropine, or fluoxetine. CPZ induced ptosis at doses of 10 and 30 mg/kg and risperidone induced ptosis at 1 mg/kg when given alone. When administered with CPZ and risperidone, aripiprazole augmented the effects of either drug alone. The effect was marked with risperidone and only slight with CPZ. When lorazepam and aripiprazole were given in combination, ptosis was observed at all doses of lorazepam [similar incidence at all doses], although ptosis was not observed with either drug alone.

HAL, CPZ, risperidone, and fluoxetine, when administered alone, produced increases in plasma prolactin. Benztropine alone had no effect on plasma prolactin, and lorazepam alone markedly decreased plasma prolactin. Aripiprazole alone significantly increased plasma prolactin in 4/6 experiments. When aripiprazole was administered in combination with HAL, there was a slight [30%] attenuation of plasma prolactin when compared with high-dose HAL alone, but aripiprazole had no effect on risperidone-induced increases in serum prolactin. Aripiprazole completely antagonized CPZ-induced increases in plasma prolactin. Lorazepam attenuated aripiprazole-induced increase in plasma prolactin. Fluoxetine had no effect on the aripiprazole-induced increase in plasma prolactin. Benztropine in combination with aripiprazole did not significantly affect the response observed with aripiprazole alone.

METABOLITES

Eleven metabolites of aripiprazole were tested for *in vitro* binding affinity for dopamine D_2 and D_3 receptors. The data were summarized in the following sponsor's table:

Table 2

Affinity of Aripiprazole and its Metabolites and Comparators for Dopamine D_2 and D_3 Receptors

Compound	D_2 K_i (nM)	D_3 K_i (nM)
Aripiprazole	0.3	0.8
OPC-14857	0.4	0.5
DM-1458	0.7	0.4
DM-1451	0.3	0.3
DM-1452	0.3	0.4
D-CPP	126.8	41.5
DM-1454	490.8	92.1
DM-1456	957.7	7,690
DM-1455K	> 15,000	2,420
DM-1457	18% binding @ 100 μM	15% binding @ 100 μM
OPC-3952	no binding @ 100 μM	no binding @ 100 μM
OPC-3373	no binding @ 100 μM	no binding @ 100 μM
haloperidol	0.4	ND

D_2 receptor binding determined utilizing [^{3}H]-raclopride binding in rat striatum; D_3 receptor binding determined utilizing [^{3}H]-7-hydroxy-N,N-di-n-propyl-2-amino-tetralin binding to human recombinant D_3 receptors expressed in CHO cells (Data from BMS DCNs 920008551, 920008400, 920001538, 920008550)
ND = not determined

In a separate study, metabolite, OPC-14857, was tested for *in vitro* binding affinity for a number of receptors, including the dopamine D_3, serotonin [$5HT_{1A}$, $5HT_{2A}$, and $5HT_{2C}$], α_1-adrenergic, and muscarinic [M_1, M_2, M_3] receptors. In that study, OPC-14587 exhibited moderate affinity for the D_3 receptor [K_i = 29.7] and the serotonin receptors [K_i = 26.3, 38.2, 28.7, and 78.7 nM for the $5HT_{1A}$, $5HT_{2A}$, $5HT_{2C}$, and $5HT_3$ receptors, respectively], weak affinity for the $D_{4.4}$, β-adrenergic, and H_1 receptors [K_i = 133, 297, and 229 nM, respectively], and little or no affinity for the α_1- or α_2- adrenergic, cholinergic muscarinic [M_1, M_2, M_3], or σ_1 and σ_2 receptors [K_i > 1000 nM].

Selected metabolites were also assessed in functional assays. In an assay assessing D_2 agonist effects, aripiprazole, OPC-14857, and DM-1458 significantly inhibited reserpine-induced increases in DOPA accumulation in mouse forebrain [ED_{50} = 0.074, 0.082, and 0.46 mg/kg i.v., respectively], whereas OPC-3952, DCPP, and DM-1454 had less activity in this assay [47.4, 39, and 45-50% inhibition, respectively, at 1 mg/kg i.v.] DM-1451 [0.03-0.3 mg/kg i.v.], DM-1452 [0.03-0.3 mg/kg i.v.], OPC-3373 [1 mg/kg i.v.], DM-1456, DM-1457, and DM-1455K had no effect at the doses tested.

In an assay assessing D_2 antagonist effects, OPC-14857 and DM-1451 inhibited apomorphine-induced stereotypy [ED_{50} = 0.066 and 0.073 mg/kg i.v., respectively] at doses comparable to those of aripiprazole [ED_{50} = 0.081 mg/kg i.v.].DM-1452 significantly inhibited apomorphine-induced stereotypy at 1.0 mg/kg i.v. OPC-3373, DM-1454, DM-1456, DM-1457, DM-1458, DM-1455K, OPC-3952, and DCPP [1 mg/kg i.v.] had no effect at the dose(s) tested.

In C6 glioma cells transfected with the rat D_{2L} receptor, DM-1451[a major rodent metabolite] inhibited isoproterenol-induced cAMP production. Alone, DM-1451 had no effect on cAMP production. This would suggest a D_2 antagonist effect.

The functional effect of metabolites, OPC-14857 and OPC-3373, [characterized as major metabolites] were tested *in vitro* in isolated [male Hartley] guinea pig ileum and ileal longitudinal muscle. Neither compound had a direct effect on resting tension at concentrations up to 10^{-5} M. OPC-14857 antagonized ACh-induced contractions at the highest concentration tested [10^{-5} M] and histamine-induced contractions at all concentrations tested [$pA_2 = 8.13 \pm 0.25$; $pD_2 = 4.88 \pm 0.08$]. OPC-14857 had no effect on barium-induced contractions. OPC-3773 had no effect on ACh- or histamine-induced contractions. OPC-3373 slightly, but significantly augmented barium-induced contractions at 10^{-5} M.

The effect of metabolites, OPC14857 and OPC-3373, on body temperature was assessed in male Wistar rats. Neither compound has a significant effect on rectal temperature following i.v. dosing [0.1-1 mg/kg].

Pharmacology Summary and Conclusions

The sponsor has characterized aripiprazole as a D_2 and $5HT_{1A}$ partial agonist, and a $5HT_2$ antagonist. However, the data provided indicate that the pharmacology of aripiprazole is complex and somewhat contradictory. In *in vitro* receptor binding assays, aripiprazole exhibited highest affinity for the D_2, D_3, and $5HT_{1A}$ receptors, high affinity for the $5HT_{2A}$ and $5HT_{2C}$ receptors, and moderate affinity for the α_1-adrenergic and H_1 receptors. Partial agonist activity at the D_2 and $5HT_{1A}$ receptors was observed in *in vitro* and *in vivo* functional studies. [Functional effects at the D_2 receptor were studied more extensively than those at the $5HT_{1A}$ receptor.] Aripiprazole exhibited agonist effects at these receptors, but with maximal effects less than those of full agonists. In addition, aripiprazole was shown to inhibit the effects of dopamine *in vitro* to an extent similar to the maximal effect of aripiprazole alone. Aripiprazole also exhibited sensitivity to decreases in receptor reserve similar to a partial agonist and did not appear to increase dopamine receptor density with repeated dosing.

However, in several models of dopamine receptor supersensitivity, no D_2 agonist effects were demonstrated. Aripiprazole did not induce rotational behavior in 6-OHDA or kainic acid lesioned animals or increase spontaneous motor activity in reserpine-treated animals. Aripiprazole exhibited D_2 antagonist-like effects in *in vitro* and *in vivo* studies. Aripiprazole significantly inhibited the increase in spontaneous motor activity induced by methamphetamine and antagonized apomorphine-induced spontaneous motor activity and stereotypy. Aripiprazole also inhibited the conditioned avoidance response in rats, an effect thought to have predictive validity for a clinical antipsychotic response. Although D_2 antagonist and D_2 partial agonist effects cannot be differentiated in such studies, it was notable that the effect-doses of aripiprazole were similar to those of other D_2 antagonists [e.g., chlorpromazine]. It is also notable that aripiprazole inhibited ipsilateral rotations induced by kainic acid.

Aripiprazole increased turnover of dopamine in mouse and rat brain [frontal cortex, striatum, limbic forebrain], similar to the effects of D_2 antagonists, chlorpromazine, haloperidol, and risperidone [assessed in rat brain]. The acute effects of aripiprazole were attenuated with repeated dosing. However, in olfactory tubercle, aripiprazole had no effects on dopamine metabolism following acute dosing, but

increased dopamine release with repeated dosing. Aripiprazole had no notable effects on NE or dopamine uptake in mouse forebrain.

Aripiprazole inhibited the head-twitch response induced by a $5HT_2$ agonist, indicating a $5HT_2$ antagonist effect.

The side-effect liability of aripiprazole was assessed by investigating changes in *c-fos* expression in various regions of rat brain and in induction of catalepsy in animals. Aripiprazole did not induce *c-fos* expression in the neostriatum, consistent with a reduced eps liability. However, aripiprazole also did not induced *c-fos* expression in the N. accumbens. Induction of *c-fos* expression in the N. accumbens is thought to reflect antipsychotic efficacy, and was observed with all the other antipsychotic drugs tested, including haloperidol and clozapine. Aripiprazole induced catalepsy in mice and rats following acute and repeated dosing.

The pharmacological activity of a number of metabolites was tested. Five of 11 metabolites tested demonstrated high *in vitro* binding affinity for the D_2 and D_3 receptors. Three metabolites, OPC-14857, DM-1458, and DM-1451 were found to have functional effects in *in vitro* and *in vivo* assays. OPC-14857, the major human metabolite, significantly inhibited reserpine-induced increases in DOPA accumulation in mouse forebrain and inhibited apomorphine-induced stereotypy at doses similar to those of aripiprazole.

Labeling recommendations: the following revisions to the sponsor's proposed labeling are recommended:

CLINICAL PHARMACOLOGY
Pharmacodynamics

Aripiprazole exhibited high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7 and 3.4 nM, respectively); and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM respectively) **and the serotonin reuptake site (K_i = 98 nM). Aripiprazole had no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1000 nM).** Aripiprazole functioned as a partial agonist at the dopamine D_2 **and the serotonin 5-HT1A receptors, and as;**

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown.

II. SAFETY PHARMACOLOGY

ARIPIPRAZOLE

Neurological effects

The sponsor conducted a number of studies to assess the CNS effects of aripiprazole. The findings from these studies are summarized.

1. Report No. 005177 [Study No. 006145]: the behavioral effects of aripiprazole were tested at doses of 0.1-100 mg/kg p.o. in male ICR mice using the Irwin screen. Observations were recorded prior to dosing and at 0.5, 1, 2, 4, 6, and 8 hrs [and at 24 hrs in selected animals]. Additional animals were treated with haloperidol [HAL] or chlorpromazine [CPZ] [0.1-100 mg/kg p.o.].

Five of 10 mice died following the 100-mg/kg dose of HAL. There were no deaths in aripiprazole- or CPZ-treated animals. No adverse effects were observed with aripiprazole or HAL at the LD [no data were provided at the LD for CPZ]. With aripiprazole, the only alertness was affected at 1 mg/kg; at 10 mg/kg, effects on alertness and response to touch and catalepsy [9/10] were observed at 10 mg/kg. At the HD, numerous effects were noted [i.e., twitches, ptosis, catalepsy, and abnormal gait, and effects on body position, alertness, response to touch, skin color, body tone, grip strength, spontaneous motor activity, flexor and righting reflexes]. With CPZ, effects on alertness and response to touch were observed at all doses [dose-related incidence]. Effects on body position, pinna reflex, skin color, body tone, grip strength, and spontaneous motor activity, and twitches, ptosis, passivity, catalepsy [2/10 at 10 mg/kg], abnormal gait were observed at 10 and 100 mg/kg. Observed only at the 100 mg/kg were restlessness, Straub tail, convulsions [2/10], salivation, and effects on limb tone, corneal, flexor, and righting reflexes. With HAL, altered alertness and response to touch and catalepsy were observed at doses of 1-100 mg/kg. Altered body position/tone and spontaneous motor activity and ptosis were observed at doses of 10 and 100 mg/kg. Effects observed only at the HD included primarily vocalization, restlessness, tremor, twitches, convulsions [5/5], writhing, altered pinna reflex, altered skin color, altered grip strength, abnormal gait, and loss of righting reflex.

All three compounds induced jumping, sedation [all animals], hypothermia [all animals], and altered respiration [i.e., reduced respiratory rate] at 100 mg/kg. HAL and CPZ produced sedation in 10/10 and 9/10 animals, respectively, receiving the 10-mg/kg dose, whereas on 1/10 animals treated with aripiprazole at this dose was affected. Miosis was observed at all doses of HAL; pupil size was not affected by aripiprazole or CPZ.

2. Report No. 005219 [Study No. 006327]: spontaneous motor activity [SMA] was assessed in male ICR mice following administration of aripiprazole [0.1-30 mg/kg p.o.] and CPZ [0.1-10 mg/kg p.o.]. Both compounds significantly reduced SMA; however, aripiprazole was more potent than CPZ [ED_{50} = 0.2 and 1.0 mg/kg, respectively]. The maximum effect was fairly similar with the two compounds.

3. Report No. 005066 [Study No. 006194]: effects on motor behavior [rotarod performance, traction test] were assessed in male ICR mice following administration of aripiprazole [1-100 mg/kg p.o.], CPZ [1-10 mg/kg p.o.], and HAL [1-10 mg/kg p.o.]. Rotarod performance was assessed at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdosing. For the traction test, mice were "suspended by their forepaws" from a tightly stretched wire; time to bring the hindpaws to the wire was assessed at 0.5, 1, 2, 4, 6, 8, and 24 hrs postdosing. Aripiprazole impaired rotarod performance at all doses at 0.5-8 hrs postdosing; effects at 24 hrs were observed only at 30 [1/10] and 100 [7/10] mg/kg. CPZ and HAL also impaired rotarod performance at all doses. With CPZ, only 2/10 animals were affected [only at 2 hrs postdosing]; no effects were observed at 24 hrs postdosing. With HAL, effects were observed at 0.5-8 hrs postdosing; only 1/10 HDM was

affected at 24 hrs postdosing. Muscle relaxant effects [traction test] were observed with aripiprazole at doses of 10-100 mg/kg, and with CPZ and HAL at all doses [only 1/10 animals affected at 1 mg/kg].

4. Report No. 005223 [Study No. 006370]: effects of aripiprazole and CPZ on hexobarbital-induced sleep time was tested in male ICR mice at doses of 1, 3, and 10 mg/kg p.o. The sponsor noted that aripiprazole alone did not produce loss of righting reflex. At doses of 3 and 10 mg/kg, aripiprazole and CPZ prolonged hexobarbital-induced sleep time. CPZ had a somewhat greater effect on sleep time than aripiprazole [43 and 57% vs 68 and 140% for CPZ at doses of 3 and 10 mg/kg, respectively].

5. Report No. 011698 [Study No. 014064]: the analgesic potential of aripiprazole was tested using the acetic acid writhing paradigm in male ICR mice. Aripiprazole was administered at doses of 0, 3, 10, 30, and 100 mg/kg p.o.; pretreatment time was 1 hr [T_{max} at 30 mg/kg was 1 hr]. Aripiprazole inhibited acetic acid-induced writhing at doses of 10 mg/kg and above. The sponsor noted that CPZ and HAL also are active in this paradigm [ED_{50} = 2.0 and 1.9 mg/kg p.o., respectively; previous study].

6. Report No. 004883 [Study No. 005880]: the proconvulsant effects of aripiprazole [10, 30, 100 mg/kg p.o.] were tested in male ICR mice. Aripiprazole's effects on PTZ, strychnine, and ecs-induced convulsions were also tested. CPZ [10, 30, 100 mg/kg p.o.] and HAL [10, 30, 100 mg/kg p.o.] were tested for comparison [with strychnine]. Aripiprazole did not induce convulsions when given alone. Aripiprazole also had no clear effect on "minimal" ecs-induced convulsions [7 mM, 100 Hz, 1 msec for 0.2 sex]; 2/10 C and 3/10 per dose grp exhibited convulsions following ecs. Aripiprazole augmented PTZ-induced at doses of 30 and 100 mg/kg [2/10, 0/10, 4/10, and 4/10 animals exhibited convulsions in C, LD, MD, and HD grps, respectively]. Aripiprazole had the greatest effect on strychnine-induced convulsions [0/10, 0/10, 2/10, and 10/10 animals exhibited convulsions in C, LD, MD, and HD grps, respectively]. CPZ also augmented strychnine-induced convulsions at the MD and HD [1/10, 5/10, 9/10 animals exhibited convulsions in LC, MD, and HD grps, respectively]. Haloperidol resulted in severe clinical signs ["shivering, lateral dislocation, and collapse"] at the HD; 2 animals were not tested with strychnine. HAL showed an augmenting effect at the HD [0/10, 1/10, 3/8 animals exhibiting convulsions at LD, MD, and HD, respectively].

7. Report No. 005787 [Study No. 006930]: aripiprazole's effect on caudate spindle and afterdischarges following hippocampal stimulation [via chronic electrode implants] were tested in the conscious male New Zealand White rabbit at doses of 0.1, 0.3, 1, and 3 mg/kg i.v. HAL [0.01, 0.1, 0.3, and 1 mg/kg i.v.] and CPZ [0.1, 0.3, 1, and 3 mg/kg i.v.] were tested for comparison. Seven days following surgery, the caudate nucleus [0.25 Hz, 2 msec pulses] and hippocampus [50 Hz, 0.5 msec pulses] were electrically stimulated for 5 sec. For assessment of the effect on caudate spindle, voltages [baseline and threshold] were determined prior to dosing and 10 and 30 min after each dose. Sequential doses [starting with the lowest dose] were administered 1 hr apart. For assessment of the effect on hippocampal afterdischarges, afterdischarges were elicited at 10 and 30 min postdosing. Doses of aripiprazole were administered 1 hr apart, starting at the lowest dose; stimulations were delivered ≥20 min apart.

Aripiprazole had little or not effect on caudate spindle burst patterns at the doses tested. Neither HAL nor CPZ had any effect at doses ≤0.3 mg/kg. At 1 mg/kg, HAL reduced the threshold voltage "slightly". CPZ significantly reduced the threshold voltage at 1 and 3 mg/kg i.v. [1 mg/kg: 19 and 24% at 10 and 30 min postdosing, respectively; 3 mg/kg: 26 and 34% at 10 and 30 mg/kg, respectively]. According to the sponsor, these data suggest that aripiprazole [at doses up to 3 mg/kg i.v.] has "...little effect on the cerebral nuclei (caudate nucleus) or reverberating circuit of the cerebral cortex".

Aripiprazole had no consistent effect on the duration of afterdischarges following hippocampal stimulation [stimulation alone resulted in afterdischarges which spread to the cortex, resulting in convulsions in "some of the animals"]. HAL had no effect at doses ≤0.3 mg/kg, but "tended to shorten

the duration" at 30 min postdosing at 1 mg/kg. CPZ had no consistent effect; however, the sponsor noted that "...at 3 mg/kg...chlorpromazine slightly tended to potentiate the amplitude of afterdischarges in all 3 animals..."

8. Report No. 004944 [Study No. 005832]: aripiprazole's effect on EEG and sleep-wakefulness cycles was assessed in male New Zealand White rabbits at doses of 0.3 and 3 mg/kg i.v. HAL [0.3, 3 mg/kg i.v.] and CPZ [3 mg/kg i.v.] were tested for comparison. Drug effects were assessed at least 7 days following implantation of chronic bipolar electrodes. Parameters were recorded prior to dosing and until 8 hrs postdosing. Aripiprazole had no effect on behavior and no "remarkable" effect on EEG at 0.3 mg/kg. However, aripiprazole produced slow-wave sleep cycles immediately upon dosing at both doses. The sponsor noted that sleep cycle patterns "resumed to normal" at 4-5 hrs after the LD and 6-8 hrs after the HD. However, it was also noted that "At 8 hr, the cycles for both doses were characterized by a decreased duration of wakefulness, an increased duration of drowsiness and slow-wave sleep and a marked decreased duration of paradoxal [sic] sleep..."

HAL had no notable effects at 0.3 mg/kg. At 3 mg/kg, HAL produced convulsions which were evident immediately following dosing and up to 10 min postdosing. Thereafter, animals appeared lethargic for about 1 hr postdosing. The effect on EEG was marked and was characterized as follows: "...remarkable high-amplitude fast waves appeared in the EEG of the amygdala from immediately after dosing until 10 minutes postdosing. Thereafter, an increase of high-amplitude, low-frequency waves were seen in the EEG of the cortex, amygdala, and posterior-hypothalamic area". HAL also decreased the duration of wakefulness and paradoxical sleep, and increased the duration of slow-wave sleep at 3 mg/kg.

CPZ produced intense sedation at 3 mg/kg, which continued up to 6-7 hrs postdosing. EEC changes, noted immediately after dosing, "...consisted of extremely low-frequency waves with a high amplitude..." and were "...similar to those of a normal sleep pattern..." up to 7-8 hrs postdosing. On sleep-wakefulness cycles, "...wakefulness was reduced, slow-wave sleep was increased, and paradoxical sleep disappeared". A decrease in heart rate was noted from 30 min to 2 hrs postdosing. It was noted that the maximum hr effect, "...the heart rate was about half that of normal and was accompanied by arrhythmia".

9. Report No. 005003 [Study No. 005966]: aripiprazole's effect on EEG arousal was tested in male New Zealand White rabbits at doses of 0.1, 0.3, 1, and 3 mg/kg. CPZ [0.1, 0.3, 1, 3 mg/kg i.v.] and HAL [0.03, 0.1, 0.3, and 1 mg/kg i.v.] were tested for comparison. Electrodes were chronically implanted in the motor, sensory, and visual cortices, and the subcortical hippocampus for recording and the mesencephalic reticular formation [MRF] for delivery of electrical stimulation. Drugs were administered at least 7 days following surgery. Doses were administered once per hr, starting at the lowest dose. EEG arousal responses were recorded 30 min after electrical and auditory stimulation.

All three compounds exhibited a dose-related increase in threshold voltage of EEG arousal response induced by MRF stimulation. Aripiprazole increased the threshold voltage at and 3 mg/kg] effect on EEG arousal induced by electrical stimulation of the MRF; however, the effect was significantly only at the HD [17%]. HAL increased the threshold voltage at all doses; however, the effect was significantly only at 0.3 and 1 mg/kg [15 and 18%, respectively]. CPZ increased the threshold voltage at doses of 0.3-3 mg/kg, with the effect being significant only at the HD [16%].

Aripiprazole inhibited the EEG arousal response to auditory stimulation at 1 and 3 mg/kg. The effect of HAL on EEG arousal following auditory stimulation was unclear. Some evidence of stimulation was noted at all doses; however, the duration of the response was characterized as short with a rapid return to a "drowsiness pattern" following termination of the auditory stimulus. CPZ inhibited the EEG arousal response to auditory stimulation at all doses tested.

10. Report No. 005405 [Study No. 006106]: aripiprazole's effect on "the recruiting response to electrical stimulation of the nucleus centralis medialis of the thalamus and on the augmenting response to electrical stimulation of the nucleus ventralis posterolateralis of the thalamus" was tested in male New Zealand White rabbits at doses of 0.1, 0.3, 1, and 3 mg/kg i.v. CPZ [0.1, 0.3, 1, and 3 mg/kg i.v.] and HAL [0.03, 0.1, 0.3, and 1 mg/kg i.v.] were tested for comparison. Chronic electrodes were implanted in the motor and sensory cortices and the subcortical hippocampus for recording, and in the nucleus centralis medialis and the nucleus ventralis posterolateralis of the thalamus for delivery of electrical stimulation. At least 7 days following dosing, drugs were administered [in increase doses] at least 1 hr apart; threshold voltages were determined at 11-45 min postdosing.

Following low-frequency electrical stimulation of the nucleus centralis medialis of the thalamus, active recruiting voltages were detected primarily in the motor cortex. All three compounds has little or no effect on the threshold voltage. Low-frequency electrical stimulation of the nucleus ventralis posterolateralis of the thalamus resulted in augmenting responses only in the sensory cortex. All three compounds had little or no effect on the threshold voltage.

11. Report No. 005160 [Study No. 006052]: the effect of aripiprazole on neuromuscular and sympathetic ganglion neurotransmission was tested in anesthetized male cats at doses of 0.1, 0.3, 1, and 3 mg/kg i.v. For comparison, CPZ was administered at doses of 0.01, 0.03, 0.1, 0.3, and 1 mg/kg i.v. to another grp of cats. Each cat received all doses, in increasing doses.

Aripiprazole had no effect on contraction of the tibialis anterior muscle induced by electrical stimulation of the peroneal nerve, but inhibited contraction of the nictitating membrane induced by stimulation of the superior cervical ganglion [maximum effect at 3 mg/kg, 45%]. Blood pressure was reduced at all doses, in a dose-related manner [7.6, 12.2, 22.8, and 47.2 mm Hg at 0.1, 0.3, 1, and 3 mg/kg i.v., respectively]. Heart rate was reduced at the higher doses [8 and 17 bpm at 1 and 3 mg/kg, respectively].

CPZ had no notable effect on contraction of the tibialis anterior muscle, but inhibited contraction of the nictitating membrane [maximum effect at 1 mg/kg, 90%]. Blood pressure was reduced at doses of 0.03 mg/kg and above [maximum effect at 1 mg/kg, 59.3 mm Hg]. Heart rate was not notably affected.

Cardiovascular/pulmonary effects

1. Report No. 013047 [Study No. 015415]: effects of aripiprazole [lot no. 1H98M], risperidone, and HAL on the following cardiovascular parameters were assessed in 7 isolated, canine [mongrel] heart preparations: sinus rate [SR], coronary flow, contractile force [CF]. Animals were sacrificed, hearts were rapidly removed, and sinoatrial node [entire right atrium] and papillary muscle [anterior papillary muscle of the right ventricle attached to the interventricular septum] preparations were isolated. Following injection of vehicle [10, 33.3, 100 µL], drugs were injected into either the sinus node artery of the isolated atrium or into the anterior septal artery of the isolated ventricle at increasing doses. Aripiprazole, risperidone, and HAL were tested at doses of 3, 10, 30, 100, and 300 µg.

All three drugs produced dose-related decreases in SR [aripiprazole: 100, 300 µg; risperidone: 10, 30, 100, 300 µg; HAL: 10, 30 µg; maximum effects: 21, 24, and 12%, respectively, at 300 µg]. HAL resulted in complete sinus arrest at doses of 100 and 300 µg. Aripiprazole had no effect on CF. In contrast, risperidone produced significant increases in CF at doses of 3-100 µg [maximum effect: 7% at 30 µg], and HAL produced significant decreases in CF at doses of 30-300 µg [maximum effect: 46% at 300 µg]. All three compounds produced significant increases in coronary flow at 300 µg; risperidone was slightly less efficacious than aripiprazole or HAL [97% increase vs 126% for aripiprazole and HAL].

The sponsor concluded that aripiprazole had "transient negative chronotropic properties at higher doses (100 and 300 μg) without any inotropic properties". The sponsor also noted that at the HD [300 μg], all three compounds induced coronary vasodilation.

2. Report No. 005613 [Study No. 116734]: the effect of aripiprazole on the isolated right atrium was tested in atria prepared from male Hartley guinea pigs. Arpipirazole was tested at one concentration, 3 x 10^{-3} M [doses of 10^{-6}, 3 x 10^{-6}, 10^{-5}, and 3 x 10^{-5} M]. CPZ was also tested [at the same doses] in this preparation for comparison. Parameters measured consisted of the following: contractile force [CF], beating rate.

Aripiprazole had no effect on CF, whereas CPZ inhibited CF by 50% at the HD. Both aripiprazole and CPZ reduced the beating rate [and to a similar extent] at the HC.

3. Report No. 004949 [Study No. 005960]: the respiratory and cardiovascular effects of aripiprazole and CPZ were tested in anesthetized mongrel dog [5/drug]. Both drugs were tested at doses of 0.003-3 mg/kg [concentrations of 0.06-6 mg/mL for aripiprazole and 0.01-10 mg/mL for CPZ]. Doses were administered 30-60 min apart. The following parameters were recorded: respiratory rate, bp, hr, femoral artery blood flow, ECG lead II. Respiratory rate was recorded at 3-min intervals prior to start of dosing and at 0, 3, 8, 18, 27, and 57 min postdosing. The other parameters were recorded prior to dosing and at 0.5, 1, 3, 5, 10, 20, 30, and 60 min postdosing.

Aripiprazole and CPZ increased respiratory rate at the HD [≈8 and 13 breaths/3 min, respectively]. Both drugs increased hr. The maximum effect was at 1 mg/kg for aripiprazole [≈17 bpm] and CPZ [≈9 bpm]. Both drugs reduced bp to a similar extent [dose-related; maximum effect at 3 mg/kg: 54-36% (transient-sustained)]. Both drugs increased femoral blood flow [maximum effect: 38.5 mL/min at 0.3 mg/kg for aripiprazole and 13 mL/min at 0.03 mg/kg for CPZ] at lower doses, and decreased femoral blood flow to some extent at the HD [32 and 18 mL/min for aripiprazole and CPZ, respectively].

Quantitative data were not provided for ECG. The following effects were observed with aripiprazole: (a) increased negative T-wave amplitude in 1/5 dogs at 0.03 mg/kg, (b) increased negative T-wave amplitude in 2/5 dogs and "slightly prolonged" QT intervat in 1/5 at 0.1 mg/kg, (c) increased negative T-wave amplitude in 2/5, decreased positive T-wave in 2/5 dogs, decreased negative T-wave amplitude in 1/5 dogs, and "slightly prolonged" QT interval in 1/5 dogs at 0.3 mg/kg, (d) increased negative T-wave amplitude in 2/5 dogs, decreased positive T-wave amplitude in 2/5, and a "slightly prolonged" QT interval in 3/5 dogs at 1 mg/kg, and (e) increased negative T-wave amplitude in 2/5 dogs, decreased positive T-wave amplitude in 3/5, and a "slightly prolonged" QT interval in 3/5 dogs at 3 mg/kg.

The following effects were observed with CPZ: (a) decreased positive T-wave amplitude in 2/5 and "slightly prolonged" the QT interval in 1/5 at 0.01 mg/kg, (b) decreased positive T-wave amplitude in 3/5 dogs, "slightly prolonged" the QT interval in 1/5 dogs, and slightly depressed the ST segment in 1/5 dogs at 0.03 and 0.1 mg/kg, (c) decreased positive T-wave amplitude in 2/5 dogs, "slightly prolonged" the QT interval in 2/5 dogs, and depressed the ST segment in 1/5 dogs at 0.3 mg/kg, (d) decreased the positive T-wave amplitude in 2/5 dogs, increased the positive T-wave amplitude in 2/5 dogs, "slightly prolonged" the QT interval in 3/5 dogs, and depressed the ST segment in 1/5 dogs at 1 mg/kg, and (e) decreased the positive T-wave amplitude in 1/5 dogs, increased the positive T-wave amplitude in 2/5 dogs, "slightly prolonged" the QT interval in 4/5 dogs, and depressed the ST segment in 1/5 dogs at 3 mg/kg.

The sponsor concluded that aripiprazole and CPZ produced similar effects on measured parameters; however, CPZ was ≈3 times as potent as aripiprazole.

4. Report No. 013494 [Study No. 014841]: the cardiovascular effects of aripiprazole and HAL were assessed in halothane anesthetized Beagle dog. Aripiprazole and HAL were dissolved in a lactate solution for administration; both drugs were tested at doses of 0.03, 0.3, and 3 mg/kg i.v. ECG parameters were recorded from Lead II. QT interval data were corrected for hr using Bazett's formula.

Experiment 1: the following parameters were recorded continuously: systemic blood pressure, left ventricular pressure, ECG, His bundle electrogram, monophasic action potentials [MAPs], CO, effective refractory period [ERP]. For recording of MAPS, ventricular pacings were at cycle lengths of 400 and 300 msec. Following baseline recordings, aripiprazole was administered at a dose of 0.03 mg/kg given over 10 min. Parameters were recorded at 5, 10, 15, 20, and 30 min following the start of the infusion. The same procedure was followed at the higher doses of aripiprazole, except that at the HD, parameters were recorded for 1 hr postdosing. This same procedure was used for assessment of HAL. Blood samples were collected at each sampling time in order to quantitate plasma drug levels.

The following effects were observed with aripiprazole: (a) increased hr at 0.03 and 0.3 mg/kg [169 and 179 bpm (vs 142 bpm at baseline), respectively], but a decrease in hr at 3 mg/kg [128 bpm], (b) a decrease in mean bp at 3 mg/kg [107 mm Hg vs 125 mm Hg at baseline], (c) increases in the maximal upstroke velocity of the left ventricular pressure at doses of 0.03 and 0.3 mg/kg [18 and 22%, respectively]; this parameter was slightly reduced [not significantly] at 3 mg/kg. (d) CO was increased at 0.03 mg/kg [21%] and remained significantly elevated at 0.3 mg/kg [although the magnitude of the effect was not greater than at 0.03 mg/kg]; CO was decreased at 3 mg/kg [17%]. (e) decreases in TPR at 0.03 and 0.3 mg/kg [17 and 25%, respectively]; no significant effect was observed at 3 mg/kg. (f) on ECG parameters, a decrease was noted in PR interval at 0.3 mg/kg [10%], no effect on QRS width, decreases in QT interval at 0.03 and 0.3 mg/kg [10 and 14%, respectively] with no changes in QT_c, (g) inconsistent effects on atrio-His interval [decrease at 0.3 mg/kg, increase at 3 mg/kg], (h) decreases in $MAP_{90(sinus)}$ at 0.03 and 0.3 mg/kg [7 and 10%, respectively], and an increase at 3 mg/kg [10%], (h) slight decreases in $MAP_{90(CL400)}$ at 0.03 and 0.3 mg/kg [6 and 8%, respectively] and an increase at 3 mg/kg [9%], (i) decreases in $MAP_{90(CL300)}$ at 0.03 and 0.3 mg/kg [6 and 9%, respectively] and an increase at 3 mg/kg [8%]. (j) decreases in ERF (right ventricle) at 0.03 and 0.3 mg/kg [4 and 7%, respectively] and an increase at 3 mg/kg [11%]. Aripiprazole had no effect on LVEDP, His-ventricle interval, or postrepolarization refractoriness [PRR= ERF-$MAP_{90(CL400)}$].

The following effects were observed with HAL: (a) a decrease in hr at 3 mg/kg [110 bpm vs 138 bpm at baseline], (b) decreases in bp at 0.3 and 3 mg/kg [111 and 92 mm Hg, respectively, vs 124 mm Hg at baseline], (c) a decrease in the maximal upstroke velocity of the left ventricular pressure at 3 mg/kg [27%]. (d) on ECG parameters, no effect was note on PR interval, small increases in QRS width at 0.3 and 3 mg/kg [3 and 4%, respectively], increases in both QT and QT_c at 0.3 [13 and 8%, respectively] and 3 [27 and 13%, respectively] mg/kg, (e) a small increase in His-ventricle interval at 3 mg/kg [7%], (f) increases in $MAP_{90(sinus)}$ at 0.3 and 3 mg/kg [22 and 46%, respectively], (g) increases in $MAP_{90(CL400)}$ at 0.3 and 3 mg/kg [20 and 37%, respectively], (h) increases in $MAP_{90(CL300)}$ at 0.3 and 3 mg/kg [13 and 32%, respectively], (i) increases in ERF (right ventricle) at 0.3 and 3 mg/kg [14 and 34%, respectively], (j) decreases in PRR at doses of 0.3 and 3 mg/kg [-48 and -50 msec, respectively, vs -28 msec at baseline]. HAL had no effect on LVEDP, CO or atrio-His interval.

The sponsor noted that EADs were detected in 5/6 experiments with HAL at 3 mg/kg; none were detected with aripiprazole. However, it was also noted that no triggered activity following EADs was detected with HAL.

Plasma levels of aripiprazole and HAL were as follows:

Aripiprazole: C_{max} at 0.03, 0.3, and 3 mg/kg were 53, 442, and 4732 ng/mL, respectively. T_{max} at

these doses were 5, 40, and 70 min [of the total 120 min-study], respectively; these times correspond to 5, 10, and 10 min postdosing, respectively.

HAL: C_{max} at 0.03, 0.3, and 3 mg/kg were 16.13, 140.5, and 1370.83 ng/mL, respectively. T_{max} at these doses were 10, 40, and 70 min [of the total 120-min study], respectively; these times correspond to 10 min postdosing at all doses.

Experiment 2: this experiment was conducted to follow up on effects of aripiprazole observed in Experiment 1. In Experiment 2, a β-blocking agent [esmolol] was used in order to distinguish between a direct cardiostimulatory effect and an indirect effect mediated via baroreceptors in response to a drug-induced hypotension. The following parameters were continuously recorded: systemic blood pressure, ECG, MAP, ERP. Following baseline recordings, esmolol was infused at a dose previously demonstrated to "sufficiently block" β-adrenergic receptors in this animal model [i.e., 0.1 mg/kg/min]; esmolol was infused continuously throughout the testing period. Aripiprazole was infused at doses of 0.03 and 0.3 mg/kg over 10 min, beginning 30 min after the start of the esmolol infusion. Cardiovascular parameters were recorded at baseline and at 5, 10, 15, 20, and 30 min after the start of the aripiprazole infusions.

Esmolol infusion had the following effects: (a) decrease in hr with no change in blood pressure, (b) prolongation of the PR and QT intervals, with no change in QRS width or QT_c, and (c) prolongation of $MAP_{90(sinus)}$ and ERP, with no effects on $MAP_{90(CL400)}$, $MAP_{90(CL300)}$, or PRR. Esmolol infusion blocked the effects of aripiprazole on hr, bp, PR or QT interval, QRS width, MAP, ERP or PRR.

Conclusions: aripiprazole exhibited "positive chronotropic, inotropic and dromotropic effects, shortening of the ERT and repolarization phase, increase of the cardiac output, and decrease of TPR" [i.e., cardiostimulatory effects] at lower doses; however, at the HD, may effects were either attenuated or reversed. Esmolol administration block the effects of aripiprazole [at lower doses]. The sponsor attributed findings at the lower doses to nonspecific vasodilator activity, and attenuation [or reversal] at the HD via $5HT_2$-induced vasoconstriction. That esmolol blocked the effects of aripiprazole at the lower doses would suggest, according to the sponsor, that effects on cardiac function may have been secondary to vasodilation-induced effects on autonomic reflexes. The sponsor noted that aripiprazole prolonged ventricular repolarization, but only at the HD.

HAL exhibited "...hypotensive action, intraventricular conduction delay,..increases in ERP, ventricular repolarization phase and PRR were observed in addition to the further decrease of TPR..." at the MD. At the HD, HAL exhibited negative inotropic and chronotropic effects, "..potentiated effects induced by the middle dose..." while not affecting "...the preload to the left ventricle, cardiac output and atrioventricular conduction". The sponsor noted that similar findings with HAL have been previously reported. The sponsor noted that a recent study [Suessbrich H *et al. Br J Pharmacol* 120:968-974, 1997] reported that HAL blocks the I_{Kr} channel *in vitro*, and proposed this as a mechanism for the prolongation of ventricular polarization observed in this study.

Renal effects

Report No. 005044 [Study No. 005991]: the effects of aripiprazole on urine volume and electrolyte excretion were assessed in male Wistar rats following a saline load. Aripiprazole was administered orally at doses of 0, 30, 100, and 300 mg/kg. Furosemide [30 mg/kg] was administered to separate animals as a positive control. Urine samples were collected for 5 hrs following dosing. The following parameters were assessed: urinary volume, Na, K, and Cl excretion.

Aripiprazole had no significant effect on the parameters assessed, although values for all tended to be lowest at the HD [16, 36, 29, and 30% for volume, Na, K, and Cl excretion, respectively]. Furosemide

resulted in marked increases in all parameters [84, 100, 53, 110% over C values for volume, Na, K, and Cl excretion, respectively].

Gastrointestinal effects

1. Report No. 005275 [Study No. 006382]: the effect of aripiprazole on GI propulsion was tested in male ICR mice at doses of 0, 10, 30, and 100 mg/kg p.o. Aripiprazole was administered following an 18-hr fast, and 1 hr before administration of a 5% charcoal suspension. Animals were sacrificed 30 min after administration of the charcoal suspension. Atropine [30 mg/kg p.o.] was administered to separate animals as a positive control.

Aripiprazole decreased the propulsion of the charcoal meal [calculated as the distance moved/entire length of the small intestine] at all doses; the effect was significant at all but the LD [9, 10, and 19% at 10, 30, and 100 mg/kg, respectively]. By comparison, atropine inhibited propulsion by 50% at 30 mg/kg.

2. Report No. 004876 [Study No. 005901]: the effect of aripiprazole on gastric motility was tested in anesthetized male Wistar rats at doses of 0, 0.3, 1, and 3 mg/kg i.v. Spontaneous gastric motility was measured [via a transducer connected to the gastric pylorus] for 2 hrs postdosing. Gastric motility and gastric muscle tone were quantitated using a 5-point scale, from -2 [decreased] to +2 [increased]. Aripiprazole had no clear effect on either parameter measured.

3. Report No. 004896 [Study No. 005948]: the effect of aripiprazole on gastric motility was tested in anesthetized male Wistar rats at doses of 0, 0.3, 1, and 3 mg/kg i.v. The methodology was similar to that used in Study No. 005901, except that the transducer was connected to the duodenum in this study. Aripiprazole had no clear effect on amplitude. Muscle tone tended to be increased at all doses of aripiprazole [mean response: -0.3, 0.3, 0.3, and 0.5 at 0, 0.3, 1, and 3 mg/kg i.v.].

4. Report No. 005084 [Study No. 006013]: the effect of aripiprazole on gastric secretion was tested at doses of 0, 0.3, 1, and 3 mg/kg i.v. in pylorus-ligated male Wistar rats. Arpipirazole was administered immediately following ligation. Animals were sacrificed 5 hrs later and gastric juice was collected. Gastric juice volume, pH, and acid concentration were quantitated; gastric output was calculated based on volume and acid concentration. Aripiprazole had no significant effects on the parameters assessed. However, volume, acid concentration, and, therefore, acid output tended to be lower at the HD [26, 13, and 33%, respectively] compared to C. Acid concentration and acid output also tended to be lower at the MD [23 and 36%, respectively] compared to C.

Abuse liability: four studies were conducted in order to assess abuse liability; these studies were included in the Special Toxicology section.

Other

1. Report No. 004928 [Study No. 005895]: the local anesthetic and mucosal irritation potential of aripiprazole was tested in male Hartley guinea pigs. In each guinea pig, aripiprazole [0.1, 0.3% solution] was applied to one conjunctival sac and saline was applied to the other. Corneal reflexes were tested [using a mandarin wire] at 5, 10, 20, and 30 min postdosing [5 times at each sampling time]. Eyes were also examined for "...corneal opacity, appearance of the iris, severity of redness and chemosis in the conjunctiva, discharge, eye closere, and occurrence of hyperemia around the eyelids and swelling in the eyelids..." Eyes were examined in selected animals at 30 min postdosing.

Aripiprazole had no effect on corneal reflex at the doses tested. In contrast, lidocaine markedly inhibited the corneal reflex at 5 and 10 min postdosing. At both concentrations of aripiprazole, "slight" congestion

of the conjunctiva and lacrimation were observed. [These signs were also detected in vehicle-treated eyes.] In 1/5 animals at each concentration, some "white crystal-like substance" [assumed to be residual drug] was still evident at 30 min postdosing. The sponsor concluded that aripiprazole produced "only a very slight congestion of the conjunctiva".

METABOLITES

Neurological effects

1. Report 011707 [Study No. 014070]: metabolites, OPC-14857 and OPC-3373, were tested at doses of 0, 0.1 and 1 mg/kg i.v. in male ICR mice for their CNS effects using the Irwin screen. Animals were observed for 6 hrs after dosing. No effects on any parameters were observed with OPC-3373. Following the 1-mg/kg dose of OPC-14857, decreases in alertness, touch response, and spontaneous motor activity and catalepsy were observed in a majority of animals [6-7/8]; sedation was noted in 1/8 mice at 1 mg/kg. Behavior had normalized in all HD animals by 6 hrs postdosing.

2. Report No. 011811 [Study No. 014071]: the effects of metabolites, OPC-14857 and OPC-3373, on spontaneous motor activity [SMA] were tested in male ICR mice at doses of 0, 0.01, 0.1, and 1 mg/kg i.v. for OPC-14857 and at doses of 0, 0.1, and 1 mg/kg i.v. for OPC-3373. SMA was recorded at 30-min intervals for 7 hrs postdosing. OPC-14857 decreased SMA throughout the measurement period at doses of 0.1 and 1 mg/kg; at 0.1 mg/kg, the effect was fairly consistent [52-57%] whereas at the HD the effect diminished somewhat over time [81% at 0.5 hr, 46% at 7 hr postdosing]. OPC-3373 had no effect on SMA.

3. Report No. 011777 [Study No. 014105]: the effects of metabolites, OPC-14857 and OPC-3373, on hexobarbital-induced hypnosis were tested in male ICR mice at doses of 0, 0.1, and 1 mg/kg i.v. Animals were observed for 15 min postdosing for loss of righting reflex. Hexobarbital [70 mg/kg i.p.] was administered to unaffected animals. Sleep-onset time and sleep duration were recorded. Neither compound induced loss of righting reflex at the doses tested. OPC-14857 had no effect on sleep-onset time, but did prolong hexobarbital-induced sleep duration [17 and 57% at 0.1 and 1 mg/kg, respectively; significant only at 1 mg/kg]. OPC-3373 had no effect on either parameter.

4. Report No. 011761 [Study No. 014128]: the effects of metabolites, OPC-14857 and OPC-3373, on acetic acid-induced writhing were tested in male ICR mice at doses of 0, 0.1, and 1 mg/kg i.v. Acetic acid was administered i.p. 15 min after administration of either metabolite. The number of writhings was recorded from 10 to 20 min after acetic acid administration. OPC-14857 reduced the number of writhings at 1 mg/kg [50%]. OPC-3373 had no effect.

5. Report No. 011880 [Study No. 014116]: the proconvulsant potential of metabolites, OPC-14857 and OPC-3373, was tested in male ICR mice at doses of 0, 0.1, and 1 mg/kg i.v. Following administration of either metabolite, each animal was observed for the presence of convulsions for 15 min postdosing. Animals that did not convulse during this period received ecs [16 mA, 100 Hz, 0.9 msec pulses for 0.2 sec] to the auricles, PTZ [65 mg/kg i.p.], or strychnine [0.8 mg/kg i.p.]. Animals were observed for 1 hr postdosing. Neither OPC-14857 nor OPC-3373 induced convulsions or potentiated induced convulsions at the doses tested.

Respiratory/Cardiovascular effects

1. Report No. 013231 [Study No. 014135]: potential effects of metabolites, OPC-14857 and OPC-3373, on respiratory and cardiovascular parameters were tested in anesthetized male mongrel dogs [4/grp] at doses of 0, 0.01, 0.1, and 1 mg/kg i.v. Increases in hr and femoral blood flow [FBF] were observed

following the 1-mg/kg of OPC-14857; FBF was also affected at 0.1 mg/kg. The maximum effect on hr was a 21-bpm increase at 0.5 min postdosing. However, effects on hr and FBF were observed throughout the recording period, although hr tended to normalize by the end of the 60-min period. OPC-14857 slightly [12%] reduced mean blood pressure at 0.5 min postdosing, and bp tended to remain decreased through most of the measurement period. Shortening of the PR-interval was noted at 0.1-1 mg/kg. OPC-14857 had no notable effects on other parameters, e.g., QRS width, QT, amplitude of the T-wave. OPC-3373 had no effects on any parameter, except for a transient shortening of the QRS width [at 3 min postdosing] following the 1-mg/kg dose.

Renal effects

1. Report No. 011818 [Study No. 014101]: the effects of metabolites, OPC-14857 and OPC-3373, on urinary volume and electrolyte excretion were tested in male Wistar rats at doses of 0, 0.1, and 1 mg/kg i.v. An oral saline load was administered following dosing. Urine samples were collected over a 24-hr period following the oral saline load. Access to food and water was removed during the period of urine collection. Neither compound had any effects on urine volume or urinary excretion of Na, K, or Cl.

Gastrointestinal effects

1. Report No. 011920 [Study No. 014117]: the effects on metabolites, OPC-14857 and OPC-3373, on gastrointestinal propulsion were tested in ICR mice at doses of 0.1 and 1 mg/kg i.v. An activated charcoal slurry was administered to mice 15 min following dosing. Animals were sacrificed 30 min after the charcoal load. Gastrointestinal transit was calculated as the distance the charcoal traveled relative to the entire length of the small intestine. OPC-14857 inhibited GI transit at both doses [12 and 23%]; however, the effect was significant only at 1 mg/kg. OPC-3373 had no effect on GI transit.

Safety Pharmacology Summary and Conclusions

Aripiprazole: aripiprazole had significant effects on neurological function in male ICR mice. Aripiprazole decreased spontaneous motor activity and alertness [i.e., general sedative effects] and impaired motor activity over a wide range of oral doses [1-100 mg/kg]. EEG effects [e.g., increases in slow-wave sleep, threshold for arousal] observed in rabbits following i.v. dosing [0.3-3 mg/kg] were consistent with a sedative effect . Aripiprazole also induced muscular relaxation and prolonged hexobarbital-induced sleep in mice. Analgesic properties were demonstrated in mice in the acetic-acid writhing paradigm. Aripiprazole did not induce convulsions at 10-100 mg/kg p.o. when given alone, but did augment convulsions induced by PTZ and strychnine. Aripiprazole [i.v.] had no effect on neuromuscular transmission, but did inhibit superior cervical ganglion transmission in cats. Aripiprazole had no effect on the corneal reflex [i.e., no anesthetic effect] in male Hartley guinea pigs.

The cardiovascular effects of aripiprazole were assessed in *in vitro* and *in vivo* studies. Aripiprazole exhibited negative chronotropic effects in *in vitro* studies conducted in an isolated canine heart [sinoatrial node] preparation and in isolated guinea pig atrium. Aripiprazole significantly increased coronary flow in canine heart. In neither preparation did aripiprazole affect contractile force. In anesthetized mongrel dog, aripiprazole increased respiratory rate [3 mg/kg i.v.], decreased blood pressure [0.003-3 mg/kg], and increased heart rate [0.1-3 mg/kg]. Femoral blood flow was increased at lower doses, but decreased at the high dose [3 mg/kg]. ECG effects were observed at all doses, and included decreases in negative T-wave amplitude, decreased positive T-wave amplitude, and "slightly prolonged" QT. In anesthetized Beagle dog, aripiprazole exhibited differential effects at the lower [0.03-0.3 mg/kg i.v.] and high [3 mg/kg i.v.] doses. At 0.03-0.3 mg/kg i.v., aripiprazole increased hr, bp, maximum upstroke velocity [left ventricular pressure], and CO, and decreased TPR, monophasic action potentials, ERF. ECG effects consisted of decreases in PR [with no effect on QRS] and QT intervals; there was no change in QT_c. At

the high dose, the effects of aripiprazole observed at the lower doses were either not observed or were reversed. For example, hr, bp, and CO were decreased and ERF and monophasic action potentials were increased at 3 mg/kg. Therefore, as noted by the sponsor, aripiprazole exerted positive chronotropic, inotropic, and dromotropic effects at the lower doses; the opposite was evident at the high dose. The effects observed at the lower doses were inhibited by esmolol, a β-blocker, indicating a direct cardiostimulatory effect of aripiprazole at the lower doses. The sponsor noted that EADs were not detected with aripiprazole. Aripiprazole did not appear to have a notable effect on QT in these studies; however, aripiprazole's effect on the I_{Kr} channel was not assessed, nor was aripiprazole's effect on APD tested in other *in vitro* studies. [A recent published report noted (according to the abstract) that "a reduction in QT_c is reported with aripiprazole" (Goodnick PK *et al. Expert Opin Pharmacother* 3(5):479-498, 2002); whether this statement is based only on the data in dog is not known.]

Aripiprazole had no significant effect on renal function at doses of 30-300 mg/kg p.o. Aripiprazole increased GI transit time [i.e., decreased propulsion] in male ICR mice at doses of 10-100 mg/kg p.o., but had no clear effect on gastric motility in anesthetized male Wistar rat at doses of 0.3-3 mg/kg i.v. Aripiprazole had no significant effect on gastric secretion in male Wistar rats at doses of 0.3-3 mg/kg i.v.

Metabolites: the effects of OPC-14857 and OPC-3373 [characterized by the sponsor as major human metabolites] on various neurological, respiratory/cardiovascular, renal, and GI parameters were assessed. OPC-14857 had effects on behavior similar to observed with aripiprazole. OPC-14857 decreased alertness, reactivity, and spontaneous motor activity and induced catalepsy [0.1-1 mg/kg i.v.] in mice. OPC-14857 also prolonged hexobarbital-induced sleep time and exhibited analgesic activity in the acetic-acid induced writhing model. Unlike aripiprazole, OPC-14857 did not augment PTZ or strychnine-induced convulsions. In anesthetized mongrel dog, OPC-14857 increased hr [1 mg/kg] and femoral blood flow [0.1-1 mg/kg i.v.], shortened the PR-interval [0.1-1 mg/kg i.v.], and decreased bp [1 mg/kg i.v.], but had no notable effect on other parameters. OPC-14857 had no effect on renal function in male Wistar rats [0.1-1 mg/kg i.v.], but did inhibit GI transit [i.e., increased GI transit time] in ICR mice at 0.1-1 mg/kg i.v.

OPC-3373 exhibited no effect on any of the parameters assessed, except for a transient shortening of the QRS width following a 1-mg/kg i.v. dose in anesthetized mongrel dog.

APPEARS THIS WAY
ON ORIGINAL

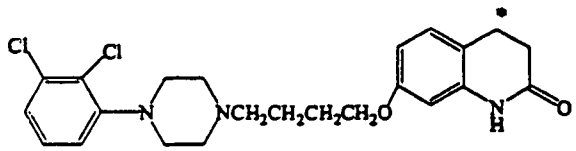
III. PHARMACOKINETICS/TOXICOKINETICS

The sponsor conducted numerous studies to assess the PK/ADME/TK of aripiprazole. The data from these studies are reviewed in this section, with the exception of the following: (a) methods validation studies and (b) studies assessing the PK/ADME/TK of aripiprazole related to the reproduction studies. The latter were reviewed by Sonia Tabascova, Ph.D. [Pharmacologist, HFD-120]; Dr. Tabascova's review is provided in the **Reproductive and Developmental Toxicology** section of this review.

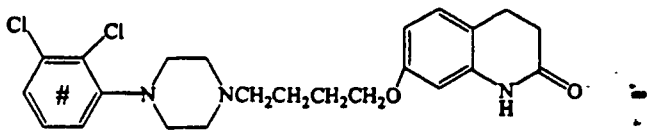
Due to time constraints, the studies summarized in this section were not reviewed in detail.

For radiolabeled studies, aripiprazole was labeled either on the quinolinone ring or the DCPP portion [phenyl ring] of the molecule. In studies using duel-labeled aripiprazole, equal portions of these radiolabeled compounds were used. The location of the label was illustrated in the following sponsor's figure:

quinoline-labeled



DCPP-labeled



PK/ADME

Mice

Plasma and intracerebral [whole brain] levels of aripiprazole following acute p.o. and i.v. administration were quantitated in male [Report No. 004683] and female [Report No. 004686] ICR mice following an 18-hr [M] or overnight [F] fast. Males received acute doses of 0.3-30 mg/kg p.o. and 3 mg/kg i.v.; females received acute doses of 10 mg/kg and 3 mg/kg i.v. Plasma data were summarized in the following sponsor's tables:

Table 5 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single oral administration of OPC-14597 at 0.3, 1, 3, 10 and 30 mg/kg to male mice

Feeding	Dose (mg/kg)	Tmax (hr)	Cmax (ng/mL)	AUC_{0-t} [3,5] (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ [5] (ng·hr/mL)	$t_{1/2}$ [5] (hr)	$t_{1/2}$ Calculated range [5] (hr)	Bioavailability [4] (%)
Fasting	0.3	0.5	29±2 [1]	137_{0-8}	229	5.9	0.5 – 8	-
	1	1.0	74±8 [2]	358_{0-8}	537	4.8	1 – 8	-
	3	2.0	161±37 [2]	997_{0-12}	1208	4.5	2 – 12	46.9
	10	2.0	608±75 [2]	3826_{0-12}	4391	3.9	2 – 12	-
	30	1.0	1431±328 [2]	17583_{0-24}	19495	7.0	4 – 24	-

1) Mean±SD, n=3, 2) Mean±SD, n=4, 3) t : terminal detected time (hr)
4) The bioavailability was calculated from the $AUC_{0-inf\ (predicted)}$ of the oral and intravenous administration at 3 mg/kg.
5) Data resulted from WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Table 6 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single intravenous administration of OPC-14597 at 3 mg/kg to male mice

Feeding	C_0 [2,4] (ng/mL)	C_{5min} [1] (ng/mL)	AUC_{0-t} [2,3,4] (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ [2,4] (ng·hr/mL)	$t_{1/2}$ [4] (hr)	$t_{1/2}$ Calculated range [4] (hr)	Cl (predicted) [4] (mL/hr/kg)	Vz (predicted) [4] (mL/kg)
Fasting	935	787±116	2356_{0-12}	2576	3.4	0.083 – 12	1164	5643

1) Mean±SD, n=3, 2) C_0 was extrapolated and calculated by $C_{0.083\ hr}$ and $C_{0.25\ hr}$, 3) t : terminal detected time (hr)
4) Data results from WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Table 7 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single oral administration of OPC-14597 at 10 mg/kg to female mice

Feeding condition	Dose (mg/kg)	Tmax (hr)	Cmax [1] (ng/ml)	AUC_{0-t} [2,3] (ng·hr/ml)	$AUC_{0-inf\ (predicted)}$ [3] (ng·hr/ml)	$t_{1/2}$ [3] (hr)	$t_{1/2}$ Calculated range [3] (hr)
Fasting	10	2.0	599±117	3198_{0-12}	3466	3.1	2 – 12

1) Mean±SD, n=4, 2) t : terminal detected time (hr)
3) Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Table 8 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single intravenous administration of OPC-14597 at 3 mg/kg to female mice

Feeding condition	C_0 [2,4] (ng/ml)	C_{5min} [1] (ng/ml)	AUC_{0-t} [2,3,4] (ng·hr/ml)	$AUC_{0-inf\ (predicted)}$ [2,4] (ng·hr/ml)	$t_{1/2}$ [4] (hr)	$t_{1/2}$ Calculated range [4] (hr)	Cl (predicted) [4] (ml/hr/kg)	Vz (predicted) [4] (ml/kg)
Fasting	1007	830±56	1967_{0-12}	2064	2.7	0.083 – 12	1453	5660

1) Mean±SD, n=3, 2) C_0 was extrapolated and calculated by $C_{0.083\ hr}$ and $C_{0.25\ hr}$, 3) t : terminal detected time (hr)
4) Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Brain levels [C_{max} ± SD, based on mean data; unit: ng/g] of aripiprazole are summarized in the following table:

ROUTE	DOSE (mg/kg)	MALES	FEMALES
p.o.	0.3	90 ± 3	
	1	319 ± 26	
	3	616 ± 43	
	10	2987 ± 594	3324 ± 850
	30	11730 ± 1936	
i.v.	3	5602 ± 232	6190 ± 997

Rats

PK: plasma and intracerebral [whole brain] concentrations of acute-dose aripiprazole were quantitated in male [Report No. 004677] and female [Report No. 004687] Sprague-Dawley rats following an overnight fast. Aripiprazole was administered to males at acute doses of 3, 10, and 30 mg/kg p.o. and 1, 3, and 10 mg/kg i.v. and to females at acute doses of 10 and 30 mg/kg p.o. and 1 and 3 mg/kg i.v. Plasma data were summarized in the following sponsor's tables:

Table 10 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single oral administration of OPC-14597 at 3, 10 and 30 mg/kg to male rats

Feeding	Dose (mg/kg)	Tmax (hr)	Cmax [1] (ng/mL)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ (ng·hr/mL)	$t_{1/2}$ (hr)	$t_{1/2}$ Calculated range (hr)	Bioavailability (%)
Fasting	3	1.0	7.9±1.2	12_{0-2}	-	-	-	-
	10	2.0	86±12	249_{0-6}	308	2.2	2 – 6	16.0
	30	4.0	442±155	3044_{0-12}	3135	1.9	4 – 12	-
Non-fasting	30	2.0	374±106	2948_{0-12}	3138	2.6	4 – 12	-

1) : Mean±SD, n=4, t : terminal detected time (hr), - : not calculated
Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).
The bioavailability of 10 mg/kg was calculated from the $AUC_{0-inf\ (predicted)}$ after a single intravenous administration at 10 mg/kg.

Table 11 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single intravenous administration of OPC-14597 at 1, 3 and 10 mg/kg to fasting male rats

Dose (mg/kg)	C_0 [2] (ng/mL)	C_{5min} [1] (ng/mL)	AUC_{0-t} [2] (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ [2] (ng·hr/mL)	$t_{1/2}$ (hr)	$t_{1/2}$ Calculated range (hr)	$Cl_{(predicted)}$ (mL/hr/kg)	$Vz_{(predicted)}$ (mL/kg)
1	211	177±34	135_{0-2}	151	0.6	0.083 – 2	6607	6034
3	636	480±76	463_{0-4}	485	0.9	0.083 – 4	6181	8129
10	1267	1218±110	1907_{0-8}	1928	1.2	0.083 – 8	5186	9183

1) : Mean±SD, n=3, 2) : C_0 was extrapolated and calculated by $C_{0.083\ hr}$ and $C_{0.25\ hr}$, t : terminal detected time (hr)
Each data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Attachment 1 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single oral administration of OPC-14597 at 10 and 30 mg/kg to female rats

Feeding condition	Dose (mg/kg)	Tmax (hr)	Cmax [1] (ng/mL)	AUC_{0-t} [2] (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ [3] (ng·hr/mL)	$t_{1/2}$ [3] (hr)	$t_{1/2}$ Calculated range [3] (hr)
Fasting	10	3.0	158±78	616_{0-8}	645	1.0	3 – 6
	30	2.0	981±201	13457_{0-24}	13548	2.4	12 – 24

1) Mean±SD, n=4, 2) t : terminal detected time (hr)
3) Data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Attachment 2 Pharmacokinetic parameters of OPC-14597 in inferior vena cava after a single intravenous administration of OPC-14597 at 1 and 3 mg/kg to fasting female rats

Dose (mg/kg)	C_0 [2,4] (ng/mL)	C_{5min} [1] (ng/mL)	AUC_{0-t} [2,3,4] (ng·hr/mL)	$AUC_{0-inf\ (predicted)}$ [2,4] (ng·hr/mL)	$t_{1/2}$ [4] (hr)	$t_{1/2}$ Calculated range [4] (hr)	$Cl_{(predicted)}$ [4] (mL/hr/kg)	$Vz_{(predicted)}$ [4] (mL/kg)
1	199	166±9	152_{0-3}	165	0.8	0.083 – 3	6068	7192
3	451	428±62	564_{0-4}	600	1.0	0.083 – 4	4998	7136

1) Mean±SD, n=3, 2) C_0 was extrapolated and calculated by $C_{0.083\ hr}$ and $C_{0.25\ hr}$, 3) t : terminal detected time (hr)
4) Data was calculated by the WinNonlin non-compartment analysis program (Ver.3.1, Pharsight).

Brain levels [C_{max} ± SD, based on mean data; unit: ng/g] of aripiprazole are summarized in the following table:

ROUTE	DOSE (mg/kg)	MALES	FEMALES
p.o.	3	40 ± 3	
	10	390 ±57	812 ± 360
	30	2232 ± 673	12670 ± 3711
i.v.	1	1606 ± 39	1187 ± 187
	3	6988 ± 1126	5911 ± 1050
	10	23205 ± 3191	

Plasma and brain concentrations of OPC-14597 were also assayed following repeated oral dosing [10 mg/kg, 2-wk] in male Sprague-Dawley rats [3/time point; Study No's 005726, 005727]. Blood samples were collected at 1-24 hrs following the 1st, 2nd, and 14th doses, and at 2 and 24 hrs following "other administrations". Following blood collection, animals were perfused and brains were collected. Plasma and brain levels of OPC-14597 were quantitated using a validated method [Kashiyama *et al.*]. Based on Day 1, 7, and 14 data, peak plasma and brain levels of OPC-14597 were achieved at 2-4 hrs postdosing. Peak brain levels [80-137 ng/gm] were 3-4 fold higher than peak plasma levels [21-39 ng/mL]. OPC-14597 was undetectable in both plasma and brain [except on 1 day] at 24 hrs postdosing. Brain and plasma levels of OPC-14597 remained fairly stable [based on 2-hr postdosing values] throughout most of the dosing period.

Plasma concentrations of OPC-14597 [6 and 20 mg/kg] following 2 wks of oral dosing were also assessed in male Sprague-Dawley rats [3/time point] in Study No. 007049. Blood samples were collected at 0, 2, 4, 8, and 24 hrs after the final doses, and just prior to the 10th and 13th doses [20 mg/kg only]. OPC-14597 was quantitated using a validated method [Kashiyama *et al.*]. OPC-14597 was not detectable 24 hrs postdosing at any of the time points sampled. Following the final dose, peak levels were 11.5 ± 10.4 and 38.4 ± 16.1 ng/mL in males and females, respectively, at 6 mg/kg, and 297.6 ± 34.1 and 391.9 ± 157.5 ng/mL in males and females, respectively, at 20 mg/kg.

PK/ADME following acute administration of ^{14}C-OPC-14597 [aripiprazole] was assessed in male [Report No. 005518, 005520] and female [Report No. 005516] Sprague-Dawley rats. In males, ^{14}C-OPC-14597 was administered at acute doses of 2, 3, 10, and 30-mg/kg p.o. and 3-mg/kg i.v. for quantitation of plasma exposure; elimination [urine, feces, bile] was assessed following a 3-mg/kg oral dose. In females, ^{14}C-14597 was administered at an acute dose of 3 mg/kg for quantitation of plasma, urinary, fecal, and biliary drug levels. The plasma data were summarized in the following sponsor's tables:

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